NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Lorlatinib for treating ALK-positive advanced non-small-cell lung cancer

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of lorlatinib within its marketing authorisation for treating ALK-positive advanced non-small-cell lung cancer.

Background

Lung cancer falls into 2 histological categories: around 88% are classified as non-small cell lung cancer (NSCLC), with the remaining patients classified as small cell lung cancer.[1] NSCLC may be further grouped by tumour histology into squamous cell carcinoma, adenocarcinoma and large-cell carcinoma, with the latter 2 being collectively referred to as 'non-squamous' lung cancer.

Anaplastic lymphoma kinase (ALK) fusion genes are chromosomal alterations that occur between the tyrosine kinase portion of the ALK gene and other genes. They are believed to be involved in the growth of tumours. ALK translocation can occur in NSCLC of any histology, although it is thought to be most common in tumours (almost exclusively) with adenocarcinoma histology (that is, non-squamous histology) which represent 36% of NSCLC patients and is uncommon in tumours with squamous cell carcinoma histology.[1,2]

In 2016, there were 38,381 (20,560 males and 17,821 females) cases of lung cancer registered in England[3]. Approximately 5% of people with NSCLC have ALK fusion genes[4].

For the majority of people with NSCLC, the aims of treatment are to prolong survival and improve quality of life. Treatment choices are influenced by the presence of biological markers (such as mutations in EGFR-TK, ALK or PD-L1 status, histology (squamous or non-squamous) and previous treatment experience. People with confirmed ALK-positive NSCLC are likely to be offered initial treatment with ALK-targeted treatment. 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). For adults with previously treated ALK-positive advanced NSCLC, NICE recommends crizotinib as a treatment option (NICE TA422). For adults with ALK-positive advanced NSCLC who have previously had crizotinib, NICE recommends ceritinib as an option (NICE TA395). NICE is also currently appraising brigatinib for treating ALK-positive NSCLC after crizotinib (NICE technology appraisal guidance ID1328). Atezolizumab is available as an option for adults with locally advanced or metastatic NSCLC who have previously had chemotherapy and targeted ALK treatment (NICE TA520). Pembrolizumab is available as an option for treating locally advanced or metastatic PD-L1-NSCLC in adults who have had at least one

chemotherapy and targeted ALK treatment (NICE TA428). NICE also recommends docetaxel alone for people with locally advanced or metastatic NSCLC that has progressed after chemotherapy (NICE CG121), and in combination with nintedanib for people with locally advanced, metastatic or recurrent NSCLC of adenocarcinoma histology that has progressed after first-line chemotherapy (NICE TA347). People may also receive treatment with platinum-based chemotherapy.

The technology

Lorlatinib (brand name unknown, Pfizer) inhibits the ALK and ROS1 receptor tyrosine kinases, acting against a range of ALK resistant mutations. By inhibiting ALK phosphorylation and ROS1 activity, lorlatinib inhibits the downstream signalling, inducing the apoptosis process, which results in the inhibition of tumour cells proliferation. It is taken orally.

Lorlatinib does not currently have a marketing authorisation in the UK for ALK-positive NSCLC. It has been studied in clinical trials in patients with ALK-positive and ROS1-positive advanced NSCLC (in patients with and without central nervous system metastasis).

Intervention(s)	Lorlatinib
Population(s)	People with advanced ALK-positive NSCLC

Comparators	**For people with untreated ALK-positive advanced NSCLC:** • Ceritinib • Crizotinib • Alectinib (subject to ongoing NICE appraisal) **For people with ALK-positive advanced NSCLC who have previously had 1 or more ALK-targeted treatments:** • Crizotinib • Ceritinib (for adults with advanced ALK-positive NSCLC who have previously had crizotinib) • Brigatinib (for adults with advanced ALK-positive NSCLC who have previously had crizotinib; subject to ongoing NICE appraisal) • Atezolizumab (for adults with locally advanced or metastatic NSCLC who have previously received chemotherapy and targeted ALK treatment) • Pembrolizumab (for adults with locally advanced or metastatic PD-L1-NSCLC who have head at least one chemotherapy and targeted ALK treatment) • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention or comparator technologies will be taken into account. The use of lorlatinib is conditional on ALK status. The economic modelling should include the costs associated with diagnostic testing for ALK status in people with advanced NSCLC who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the diagnostic test. See section 5.9 of the Guide to the Methods of Technology Appraisals.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy (2018) Technology Appraisal 520. Review date: May 2021. Ceritinib for previously treated anaplastic lymphoma kinase positive non-small-cell lung cancer (2016) Technology Appraisal 395. Review date: TBC. Ceritinib for untreated ALK-positive non-small-cell lung cancer (2018) Technology Appraisal 500. Review date: January 2021. Crizotinib for previously treated anaplastic lymphoma

	kinase-positive advanced non-small-cell lung cancer (2016) Technology Appraisal 422. Review date: December 2019. Crizotinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer (2016). Technology Appraisal 406. Review date: September 2019. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (2015) Technology Appraisal 347. Review date: July 2018. Nivolumab for previously treated squamous non-small-cell lung cancer (2017) Technology Appraisal 483. Review date: June 2019. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (2017) Technology Appraisal 428. Review date: January 2019. **Appraisals in development (including suspended appraisals):** Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer. NICE technology appraisal guidance [ID925]. Publication expected: August 2018. Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib. NICE technology appraisal guidance [ID1328]. Publication expected: December 2018. **Related Guidelines:** Lung cancer: diagnosis and management (2011) NICE guidelines CG121. Reviewed 2016, next review January 2019. **Related Quality Standards**: Quality standard for lung cancer. (2012) NICE Quality Standard 17. Reviewed 2016, next review August 2017. **Related NICE Pathways:** Lung cancer (2017) NICE
Related National Policy	**National Service Frameworks:** Cancer **Department of Health:** Department of Health (2013) NHS Outcomes

	Framework 2014–2015 Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance Department of Health (2007) Cancer reform strategy Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. Domains 1, 2, 4 and 5. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf **NHS England:** NHS England (2014) Manual for Prescribed Specialised Services 2013/14. Chapter 105: Specialist cancer services (adults) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf

Questions for consultation

Questions about comparators and the treatment pathway:

Where do you consider lorlatinib will fit into the existing NICE pathway 'Lung cancer'?

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?

Which treatments are people with ALK-positive advanced NSCLC likely to receive after initial treatment with ceritinib?

Which treatments are people with ALK-positive advanced NSCLC likely to receive after initial treatment with crizotinib?

Which treatments are people with ALK-positive advanced NSCLC likely to receive after initial treatment with alectinib?

What is the established clinical practice in the NHS for people who have been treated with more than 1 ALK-targeted treatment?

How should best supportive care be defined?

Would best supportive care include chemotherapy? If so, which treatment regimens? Would nintedanib be used in combination with chemotherapy?

Questions about other areas of the scope:

Are the outcomes listed appropriate?

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?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which lorlatinib will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

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)?

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?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

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.

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. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-

do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1 Royal college of physicians (2018). National Lung Cancer Audit: Annual report 2017. Accessed May 2018.

2 Scagliotti G, Stahel RA, Rosell R et al. (2012) ALK translocation and crizotinib in non-small cell lung cancer: An evolving paradigm in oncology drug development. European Journal of Cancer 48: 961-973

3 Office for National Statistics (2018). Cancer registration statistics, England: first release, 2016. Accessed May 2018.

4 Cancer Research UK (2018). About targeted cancer drugs. Accessed May 2018.