NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Ramucirumab with erlotinib for untreated EGFR-positive metastatic non-small-cell lung cancer

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of ramucirumab with erlotinib within its marketing authorisation for treating epidermal growth factor receptor (EGFR)-positive metastatic non-small-cell lung cancer that has not previously been treated.

Background

Lung cancer falls into two main histological categories: around 85–90% are non-small-cell lung cancers (NSCLC) and the remainder are small cell lung cancers[1]. NSCLC can be further classified into squamous cell carcinoma and non-squamous cell carcinoma. Approximately 70% of NSCLC are of non-squamous histology and can be either large-cell undifferentiated carcinoma or adenocarcinoma[2]. Most lung cancers are diagnosed at an advanced stage, when the cancer has spread to lymph nodes and other organs in the chest (locally advanced disease; stage III) or to other parts of the body (metastatic disease; stage IV). In 2017, 39,205 people were diagnosed with NSCLC in England & Wales, and around 65% had stage IIIB or stage IV disease[3].

Lung cancer caused over 28,500 deaths in England in 2016[4]. Thirty two percent of people with lung cancer survive for more than 1 year after diagnosis[5]. For the majority of people with NSCLC, the aims of therapy are to prolong survival and improve quality of life. Treatment choices are influenced by the presence of biological markers (such as mutations in epidermal growth factor receptor-tyrosine kinase (EGFR-TK), anaplastic-lymphoma-kinase (ALK) or PD-L1 status), histology (squamous or non-squamous) and previous treatment experience.

For people whose locally advanced or metastatic disease tests positive for the activating EGFR-TK mutation and who have not previously had treatment, NICE guidance recommends the tyrosine kinase inhibitors (TKIs) dacomitinib, afatinib, erlotinib, and gefitinib as treatment options (NICE technology appraisal guidance 595, 310, 258, and 192 respectively).

The technology

Ramucirumab (Cyramza, Lilly UK) is a fully human immunoglobulin G1 monoclonal antibody. It specifically blocks the vascular endothelial growth factor receptor-2, which plays an important role in angiogenesis (formation of new blood vessels) in tumours. Ramucirumab is administered intravenously.

Erlotinib (Tarceva, Roche Products) is an orally administered inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK). It blocks the signal pathways involved in cell proliferation and slows the growth and spread of the tumour.

Ramucirumab in combination with erlotinib does not currently have a marketing authorisation in the UK for untreated EGFR-positive metastatic non-small-cell lung cancer. It is being studied in a clinical trial compared with placebo in combination with erlotinib in people with untreated metastatic non-small cell lung cancer with activating EGFR mutations (EXON 19-Del and EXON 21 L858R).

Ramucirumab in combination with docetaxel has a marketing authorisation in the UK for the treatment of locally advanced or metastatic NSCLC in adults with disease progression after platinum-based chemotherapy.

Erlotinib has marketing authorisations in the UK for untreated locally advanced or metastatic NSCLC with EGFR activating mutations, maintenance treatment for locally advanced or metastatic NSCLC with EGFR activating mutations after chemotherapy, and for locally advanced or metastatic NSCLC after chemotherapy.

Intervention(s)	Ramucirumab with erlotinib
Population(s)	Adults with untreated metastatic NSCLC with activating EGFR mutations.
Comparators	• Afatinib • Erlotinib • Gefitinib • Dacomitinib • Osimertinib (subject to on-going NICE appraisal)
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • response duration • 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 commercial arrangements for the intervention, comparator or subsequent technologies will be taken into account. The use of ramucirumab with erlotinib is conditional on the presence of activating EGFR mutations. The economic modelling should include the costs associated with diagnostic testing for EGFR mutations in people with 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:** Afatinib for treating epidermal growth factor receptor mutation-positive locally advanced or metastatic non-small-cell lung cancer (2014) NICE Technology Appraisal 310. Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer (2012) NICE Technology Appraisal 258. Guidance on static list. Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer (2010) NICE Technology Appraisal 192. Dacomitinib for untreated EGFR mutation-positive non-small-cell lung cancer (2019) NICE Technology Appraisal 595. **Terminated appraisals:** Bevacizumab for treating EGFR mutation-positive non-small-cell lung cancer (terminated appraisal) (2017)

	NICE Technology Appraisal 436 **Appraisals in development (including suspended appraisals):** Osimertinib for untreated EGFR-positive non-small-cell lung cancer NICE technology appraisals guidance [ID1302]. Publication TBC. **Related Guidelines:** Lung cancer: diagnosis and management (2019). NICE guideline NG122. **Related Quality Standards:** Lung cancer in adults (2019). NICE quality standard 17 Related NICE Pathways: Lung cancer (2019) NICE pathway
Related National Policy	**National Service Frameworks:** Cancer **Department of Health:** Department of Health, NHS Outcomes Framework 2016-2017 Department of Health (2014) The national cancer strategy: 4th annual report Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance Department of Health (2007) Cancer reform strategy The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Chapter 105: Specialist cancer services (adults). Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domain 1. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 **Other policies** Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020

Questions for consultation

Have all relevant comparators for ramucirumab with erlotinib been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for EGFR-positive NSCLC?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom ramucirumab with erlotinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider ramucirumab with erlotinib will fit into the existing NICE pathway, lung cancer?

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 ramucirumab with erlotinib 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 ramucirumab with erlotinib 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 ramucirumab with erlotinib 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 technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1 Lung cancer incidence by morphology. Cancer Research UK. Accessed October 2019.

2 Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2016, National Cancer Institute. [Available from: https://seer.cancer.gov/csr/1975_2016/]. Accessed October 2019.

3 National Lung Cancer Audit: Annual report 2018 (for the audit period 2017) (2019). Royal College of Physicians. Accessed October 2019.

4 Lung cancer mortality statistics (2016). Cancer Research UK. Accessed October 2019.

5 Lung cancer survival statistics (2010-11). Cancer Research UK. Accessed October 2019.

