NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer

Final scope

Final remit/appraisal objective

To appraise the clinical and cost effectiveness of entrectinib within its marketing authorisation for treating ROS1 fusion-positive locally advanced or metastatic 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. ROS1 is a rare type of mutation, activated by chromosomal rearrangement in a variety of human cancers, including NSCLC. Rearrangement leads to fusion of a portion of ROS1, where resulting fusion kinases are constitutively activated and drive cellular transformation.[2] These rearrangements are more commonly found in patients who have never smoked and who have histologic features of adenocarcinoma, meaning there is a significant overlap with patients who have anaplastic lymphoma kinase (ALK)-positive NSCLC.[3,4] However, ROS1 appears mutually exclusive to ALK and other known oncogenic drivers such as EGFR, KRAS, HER-2, RET and MET aberrations. [4,5]

In 2016 approximately 32,533 people were diagnosed with NSCLC in England, of whom 53% had stage IV disease.[6] It is estimated that ROS1 rearrangements occur in around 1% of patients with NSCLC.[4]

About one-third of patients with NSCLC have disease which is suitable for potentially curative surgical resection. However, for the majority of people with NSCLC, the aims of treatment are to prolong survival and improve quality of life. NICE clinical guideline 121 recommends platinum-based chemotherapy as a first-line treatment for people with stage III or IV NSCLC and good performance status. Alternatively, people may receive pemetrexed in combination with cisplatin if the histology of the tumour has been confirmed as adenocarcinoma or large-cell carcinoma (NICE technology appraisal guidance 181). For people who are unable to tolerate a platinum combination, the clinical guideline recommends single-agent chemotherapy with docetaxel, gemcitabine, paclitaxel, or vinorelbine. For non-squamous NSCLC that has not progressed immediately following initial therapy with a NICE-recommended platinum-based chemotherapy regimen, maintenance

treatment with pemetrexed is recommended as an option (NICE technology appraisal guidance 190 and 402). For people with locally advanced or metastatic NSCLC whose disease has progressed after chemotherapy, NICE recommends docetaxel monotherapy (CG121) and nintedanib plus docetaxel for adenocarcinoma histology (TA347). For people with ROS1-positive advanced non-small-cell lung cancer, NICE recommends crizotinib for use within the Cancer Drugs Fund (TA529)[a].

The technology

Entrectinib (brand name unknown, Roche) is an oral selective inhibitor of the TRK family of proteins (TRKA, TRKB and TRKC), proto-oncogene tyrosine-protein kinase (ROS1) and anaplastic lymphoma kinase (ALK). Entrectinib turns off the signalling pathway that allows TRK, ROS1 and ALK fusion-positive cancers to grow. The population being considered in this scope is limited to those with ROS1 gene rearrangements. It is administered orally as a capsule.

Entrectinib does not have a marketing authorisation in the UK for treating people with ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer. It is being studied in a phase II single-arm basket trial (a study which is designed to test the effect of a single drug on a number of different gene mutations in a variety of different cancer types). In the trial, patients are assigned to different baskets according to their tumour type and gene fusion. It is also being studied in phase I trials.

The single-arm basket trial included people with NTRK fusion-positive advanced or metastatic solid tumours. This population will be considered in a separate NICE technology appraisal of entrectinib (ID1512).

[a] Products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf

Intervention(s)	Entrectinib
Population(s)	People with ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer

Comparators	Untreated disease:
	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin)
	  ○ with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment
	• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) (for people with adenocarcinoma or large cell carcinoma only)
	  ○ with (following cisplatin-containing regimens only) or without pemetrexed maintenance treatment
	• Single agent chemotherapy with a third-generation drug for people who cannot tolerate platinum-based therapy
	After previous chemotherapy treatments:
	• Docetaxel, with (for adenocarcinoma histology) or without nintedanib

Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • time to treatment discontinuation • 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. 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 and subsequent treatment technologies will be taken into account. The economic modelling should include the costs associated with diagnostic testing for ROS1 status in people with advanced non-small-cell lung cancer 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	If the evidence allows, consideration will be given to subgroup based on the presence or absence of brain metastases 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:** 'Alectinib for untreated ALK-positive advanced non-small-cell lung cancer (2018) NICE Technology Appraisal 536. Review proposal date August 2021. 'Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non‑small‑cell lung cancer' (Jul 2015). NICE Technology Appraisal 347. Review proposal date Jul 2018. 'Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer' (2018) NICE Technology Appraisal 529. Review proposal date April 2023. 'Pemetrexed for the first-line treatment of non-small-cell lung cancer' (2009) NICE Technology Appraisal 181. On static list. 'Pemetrexed maintenance treatment for non-squamous

	non-small-cell lung cancer after pemetrexed and cisplatin' (2016) NICE Technology Appraisal 402. Review proposal date August 2019. 'Pemetrexed for the maintenance treatment of non-small-cell lung cancer' (2010) NICE Technology Appraisal 190. On static list. 'Atezolizumab for treating non-small-cell lung cancer after platinum-based chemotherapy' (2018) NICE Technology appraisal 520. Review proposal date May 2021. 'Nivolumab for previously treated squamous non-small-cell lung cancer' (2017) Technology appraisal 483. Review proposal date June 2019. 'Nivolumab for previously treated non-squamous non-small-cell lung cancer' (2017) Technology appraisal 484. Review proposal date June 2019. **Appraisals in development:** 'Avelumab for treating non-small-cell lung cancer after platinum-based chemotherapy' [ID1146]. Expected publication date TBC. 'Brigatinib for treating ALK-positive non-small-cell lung cancer after crizotinib' [ID1328]. Expected publication date TBC. 'Lorlatinib for treating ALK-positive advanced non-small-cell lung cancer' [ID1338]. Expected publication date September 2019. **Related Guidelines:** 'Lung cancer' (2011). NICE guideline (CG121). Update in progress. Expected publication date January 2019. Related Quality Standards: 'Quality standard for lung cancer' (2012) NICE quality standard 17. **Related NICE Pathways:** Lung Cancer (2012) 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 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 (published 2016): Domains 1, 2, 4, 5. 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

References

[1] Royal College of Physicians (2015) National lung cancer audit annual report Accessed January 2017.

[2] Shaw A et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. New England Journal of Medicine 2014;371;21:1963-1971.

[3] Gainor JF, Shaw AT. Novel targets in non-small cell lung cancer: ROS1 and RET fusions. Oncologist 2013;18:865-875.

[4] Bergethon K, Shaw AT, Ou SH et al. ROS1 rearrangements define a unique molecular class of lung cancers. Journal of Clinical Oncology 2012;30:863-870.

[5] Korpanty GJ, Graham DM, Vincent MD, Leighl NB. Biomarkers That Currently Affect Clinical Practice in Lung Cancer: EGFR, ALK, MET, ROS-1, and KRAS. Frontiers in Oncology. 2014; 4:204. doi:10.3389/fonc.2014.00204.

[6] Health and Social Care Information Centre (2018) National Lung Cancer Audit annual report 2017 (for the audit period 2016). Accessed January 2019.