NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Entrectinib for treating NTRK fusion-positive solid tumours

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of entrectinib within its proposed marketing authorisation for treating NTRK fusion-positive advanced solid tumours.

Background

Solid tumours are abnormal localised masses of tissue. They can be cancerous (malignant) or not cancerous (benign) and are classified according to the type of cells that form them. The two major types of cancerous solid tumours are sarcomas and carcinomas. Sarcomas are developed from cells of muscles, bone or fat tissue and carcinomas start from the epithelial cells in the skin or tissues that line or cover internal organs. Advanced solid tumours can be locally advanced (tumour that has spread to surrounding tissues or lymph nodes but has not yet spread to other parts of the body) or metastatic (tumour that has spread to other parts of the body).

Tropomyosin-related kinase receptors (TRKs) belong to a family of growth receptors with tyrosine kinase activity. It contains three members, TRKA, TRKB and TRKC that are encoded by neurotrophic tyrosine kinase (NTRK) genes, NTRK1, NTRK2 and NTRK3, respectively. TRKs are exclusively expressed in human neuronal tissue and play an essential role in nervous system development and maintenance through activation by neurotrophins. TRK fusions occur when one of the NTRK genes becomes abnormally connected to another unrelated gene. This results in uncontrolled TRK signalling that can lead to various cancerous solid tumours.

In 2015, there were 359,960 new cases of cancer recorded in the UK with 163,444 cancer deaths[1]. Breast, prostate, lung and bowel cancer together accounted for more than half (53%) of all new cancers in the UK in 2015[2]. While many NTRK fusions are found at a lower incidence in tumours such as lung and gastrointestinal cancers, they are found in the majority of rare tumours such as secretory breast carcinoma and mammary analogue secretory carcinoma (MASC)[3] and in 30 to 50% of glioblastomas[4].

There are currently no treatment options available in the NHS that specifically target solid tumours with TRK-fusions. Current treatments for different solid tumour cancers generally include surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapy, or molecularly targeted treatment.

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 fusion cancers to grow. It is administered orally as a capsule.

Entrectinib does not have a marketing authorisation in the UK for treating people with NTRK fusion-positive advanced or metastatic solid tumours. It is being studied in a single-arm basket trial (a study which is designed to test the effect of a single drug on a single mutation in a variety of cancer types) in people with TRK fusion-positive, ROS1 or ALK advanced solid tumours.

Intervention(s)	entrectinib
Population(s)	People with NTRK fusion-positive locally advanced or metastatic solid tumours who: • have progressed following prior therapies • have no alternative standard therapies
Comparators	Established management without entrectinib
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • duration of response • 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 use of entrectinib is conditional on the presence of NTRK fusion. The economic modelling should include the costs associated with diagnostic testing for NTRK in people with advanced or metastatic solid tumours 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 evidence allows, subgroup analyses by: • tumour site • previous therapy 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	**Appraisals in development (including suspended appraisals):** [ID1299]. Larotrectinib for treating advanced solid tumours with TRK fusions. Publication date to be confirmed. **Related Guidelines:** Suspected cancer: recognition and referral (2015) NICE guideline NG12. Review date: TBC Improving outcomes for people with sarcoma (2006). NICE Cancer service guideline CSG9. Review date: TBC **Related Quality Standards:** Suspected cancer (2016). NICE quality standard QS124. Sarcoma (2015). NICE quality standard QS78.

Related National Policy	National Service Frameworks: Cancer Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 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): Domain 1. NHS England (2013) NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a. NHS England (2013) NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a. NHS England (2013) NHS Standard Contract for Cancer: Soft Tissue Sarcoma (Adult). B12/S/a.

Questions for consultation

What is the population size for NTRK fusion-positive advanced solid tumours?

Which solid tumour sites are most commonly associated with NTRK fusion mutation?

Which treatments are considered to be established clinical practice in the NHS for NTRK fusion-positive, locally advanced or metastatic solid tumours in people who:

- have progressed following prior therapies
- have no alternative standard therapies

How will entrectinib be used in clinical practice?

Would entrectinib be used differently based on tumour site?

Will testing for NTRK fusion-positive expression in advanced solid tumours be available routinely in the NHS?

Where do you consider entrectinib will fit into an existing NICE pathway?

Should any other comparators for entrectinib be included in the scope?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations' appropriate?

Are there any other subgroups of people in whom entrectinib 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 entrectinib 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 entrectinib 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 entrectinib 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).

References

1. Cancer Research UK 'Cancer Statistics for the UK'. Accessed October 2018.

2. Cancer Research UK 'Cancer Incidence Statistics'. Accessed October 2018.

3. Drilon A, Siena S, Ou S-H I, Patel M, Ahn MJ, Lee J, et al. Safety and Antitumor Activity of the Multi-Targeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib (RXDX-101): Combined Results from Two Phase 1 Trials (ALKA-372-001 and STARTRK-1). American Association for Cancer Research. (2017).

4. Amatu A, Sartore-Bianchi A and Siena S. NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. ESMO Open. (2016).