Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Larotrectinib for treating NTRK fusion-positive advanced solid tumours [ID1299]

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of larotrectinib within its 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 and extra-neuronal tissue and play an essential role in nervous system development and maintenance through activation by neurotrophins. NTRK 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[2]. 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 NTRK-fusions. Current treatments for different solid

tumour cancers generally include surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapy, or molecularly targeted treatment.

The technology

Larotrectinib (brand name unknown, Bayer) is an oral and selective inhibitor of the TRK family (TRKA, TRKB and TRKC). Larotrectinib turns off the signalling pathway that allows NTRK-fusion cancers to grow. It is administered orally as a capsule or as a liquid.

Larotrectinib does not have a marketing authorisation in the UK for treating advanced solid tumours with NTRK fusions. It is being studied in single-arm Phase I and II basket trials in children, young people and adults with NTRK fusion-positive advanced or metastatic solid tumours who have either progressed or not responded to standard therapies, are unfit for standard therapy or for whom no standard or available curative therapy exists.

Intervention(s)	Larotrectinib
Population(s)	People with NTRK fusion-positive advanced solid tumours who: • have either progressed on or not responded to prior therapies • are unfit for chemotherapy or for whom no curative therapy exists
Comparators	Established management without larotrectinib
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.

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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 larotrectinib is conditional on the presence of NTRK fusion. The economic modelling should include the costs associated with diagnostic testing for NTRK fusion in people with advanced 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 will be considered. 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):** [ID1512]. Entrectinib for treating NTRK fusion-positive solid tumours. Expected publication date: April 2020 **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 Framework: Cancer National Service Framework: Children, Young People and Maternity Services 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.

References

1. Cancer Research UK 'Cancer Statistics for the UK'. Accessed March 2019.

2. Cancer Research UK 'Cancer Incidence Statistics'. Accessed March 2019.

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).