National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: July 2018

Entrectinib for the treatment of NTRK-fusion positive solid tumours in adult and paediatric patients

NIHRIO (HSRIC) ID: 11705 NICE ID: 10011

LAY SUMMARY

Solid tumours are abnormal masses of cells which may be non-cancerous (benign) or cancerous (malignant). Some solid tumours may be caused by specific genetic changes, for example, mutation in the NTRK genes, which can affect signalling inside the cell which drives cell growth. When these signals become overactive, cells can grow out of control and form tumours. If these tumours are malignant, this can result in multiple different types of cancers, including; lung, head and neck and certain types of breast cancers.

Entrectinib is a drug taken daily as a capsule which works by blocking the NTRK genes, which signals cancer cells to become overactive and drive uncontrolled growth of these cancer cells. By blocking these signals, this may slow growth of these cancer cells. There are currently no drugs which target this specific signalling in cancer cells caused by the NTRK gene mutation, and so if licenced entrectinib would be the first drug which blocks this signalling pathway. Hence, entrectinib offers the potential to treat many different types of solid tumours that are positive to the NTRK gene mutation.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Solid tumours (NTRK-fusion positive, adults and paediatrics, locally advanced or metastatic)

TECHNOLOGY

DESCRIPTION

Entrectinib (RXDX-101) is an oral drug[1] designed to target tumours that harbour activating mutations, deletions or rearrangements to neurotropic tropomyosin receptor kinase (NTRK) 1, 2 and 3, the proto-oncogene ROS1, or anaplastic lymphoma kinase (ALK).[2 3, 4] Under normal conditions, these oncogenes regulate the flow of cellular growth signalling. However, when mutations or chromosome instability affect their DNA sequences, the resulting fusion proteins or other molecular alterations can be overactive, causing a signal cascade that drives uncontrolled proliferation. These abnormal cells then form localized tumours and eventually may acquire additional genomic events that enable them to spread to other parts of the body.[5] Upon administration, entrectinib binds to and inhibits NTRK, ROS1 and ALK, which are typically overexpressed in various cancer types. Inhibition of these kinases may result in a disruption of NTRK 1, 2 and 3, ROS1-, and ALK-mediated signalling. This leads to an induction of apoptosis and an inhibition of tumour cell proliferation in tumour cells that express these kinases of NTRK 1, 2 and 3, ROS1 and ALK.[1]

Entrectinib is in phase II development for the treatment of NTRK-fusion positive, locally advanced or metastatic solid tumours (NCT02568267).[6] The proposed dose of entrectinib is 600mg once a day taken as 100mg and 200mg capsules.[7]

Entrectinib does not currently have Marketing Authorisation in the EU for any indication.[8]

Entrectinib is currently in phase II development for the treatment of locally advanced or metastatic non-small cell lung cancer testing positive for activation ROS1 rearrangements.[9]

INNOVATION and/or ADVANTAGES

Entrectinib has a novel mechanism of action which specifically targets molecular pathways which are actionable drivers of tumour growth, thereby potentially affecting progression of malignancy.[3] The advantages of targeting a genetic abnormality is that this drug has the potential to treat a variety of cancers and so is a tumour agnostic targeted cancer therapy. [10]

There are currently no approved treatments that specifically target NTRK-fusion positive tumours, and this represents a clear unmet medical need. If licensed, entrectinib could be a specific treatment option for this patient group.[2]

DEVELOPER

Roche Products Ltd

REGULATORY INFORMATION/ MARKETING PLANS

Entrectinib was designated PRIME status in the EU for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumours in adult and paediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies in October 2017.[11]

Entrectinib is a designated orphan drug status in the USA for the treatment of NTRK fusion-positive solid tumours in September 2017.[12]

Entrectinib was designated US Breakthrough Therapy Status for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumours in adult and paediatric patients who have either progressed following prior therapies or who have no acceptable standard therapies on 15 May 2017.[13]

Entrectinib was awarded PRIME status for the treatment of NTRK fusion-positive, locally advanced or metastatic solid tumour in adult and paediatric patients who have either progressed following prior therapies or who have no acceptable standard therapy by EMA in October 2017.[14]

PATIENT GROUP

BACKGROUND

Solid tumours are abnormal masses of tissues which do not contain cysts or liquid areas, and can be benign or malignant. Different types of solid tumours are named after the type of cells that comprise them e.g. sarcomas, carcinoma and lymphomas.[15]

The TRKs (tropomyosin receptor kinase) receptor family comprises three transmembrane proteins, TRK A, B and C which are encoded by the neurotrophic tropomyosin receptor kinase (NTRK)1, NTRK2 and NTRK3 genes. TRKs play a key role in the development of the central and peripheral nervous system and in cell survival. Gene fusions of NTRK genes are the main molecular alterations with known oncogenic potential. In all TRK oncogenic gene fusions, the 3' region of the NTRK gene is joined with the 5' sequence of a fusion partner gene by intrachromosomal or interchromosomal rearrangement.[3] In the rearranged state, the activated fusion kinases signal through the RAS-RAF-MEK-ERK, PI3K-AKTmTOR, and PLCγ-PKC pathways, driving the initiation and progression of malignancy.

These fusions have been detected in a variety of tumours, including lung, gastrointestinal, head and neck, thyroid, spitzoid cancers, sarcomas, primary brain tumours and acute myeloid leukaemia (AML). While many of these events 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), where the identification of an NTRK fusion is a defining factor for diagnosis.[16]

Genomic changes, such as gene fusions, can be caused by many factors including external factors, such as radiation exposure, tobacco and ultraviolet light, and internal factors, such as faulty DNA repair processes.[17]

CLINICAL NEED and BURDEN OF DISEASE

NTRK1 fusion oncogenes have been identified in many types of cancer, including thyroid cancer (12%), glioblastoma (2.5%), lung cancer (1%) and many others.[18, 19]

The prevalence and incidence of NTRK fusions in cancer vary with the type of cancer. Prevalence of NTRK fusions in 408 colorectal cancer samples showed a 0.5% prevalence of NTRK fusions. A molecular screening programme reported 4% (2 of 49 cases) incidence of NTRK unidentified fusion in appendiceal adenocarcinoma. Another study stated that 3.3% of a sample of NSCLC patients harboured NTRK rearrangements potentially susceptible to TRKA inhibitors. Somatic rearrangements in the NTRK1 gene in papillary thyroid carcinoma usually don't exceed 12% however this varies between populations (from 15-50% in Italian populations to <10% in French, Japanese and Chinese). A study of 127 samples of paediatric high grade glioma (HGG) showed 40% of non-brainstem (HGG) has recurrent fusions in NTRK1, 2 or 3. NTRK3 gene fusion is a genetic feature of human secretory breast carcinoma.[3]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Larotrectinib for treating advanced solid tumours with TRK fusions [1299]. Expected publication date TBC.
- NICE quality standard. Suspected cancer (QS124). June 2016.
- NICE quality standard. Sarcoma (QS78). January 2015.
- NICE quality standard. Cancer services for children and young people (QS55). February 2014.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.
- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015.
- NICE cancer service guideline. Improving outcomes for people with sarcoma (CSG9). March 2006.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Soft Tissue Sarcoma (Adult). B12/S/a.

OTHER GUIDANCE

- NHS England. Improving outcomes through personalised medicine. 2016.[20]

CURRENT TREATMENT OPTIONS

There are multiple treatment options currently available for the generic treatment of solid tumours which include surgery, chemotherapy, radiotherapy, hormone therapy, immunotherapies (e.g. monoclonal antibodies) and targeted cancer drugs (e.g. cancer growth blockers). The treatment provided will vary according to type of cancer, how big the cancer is, of it has spread and according to the patients' general health.[10]

Regarding specific treatment for NTRK positive solid tumours, there are currently no licenced TRK inhibitors licenced for the treatment of TRK fusion positive cancers.[21]

EFFICACY and SAFETY	
Trial	STARTRK-2, NCT02568267, 2015-003385-84; entrectinib; phase II
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[6], abstract[7], publication[4]
Location	8 EU countries (including the UK), USA, Australia, Hong Kong, Japan, Republic of Korea, Singapore, Taiwan
Design	Non-randomised, open label, uncontrolled, parallel assignment, basket study
Participants	n=300 (planned); aged 18 years and older; solid tumour; NTRK1/2/3, ROS1 or ALK gene rearrangement; locally advanced or metastatic
Schedule	Participants are placed into study arms according to genetic mutation and cancer type as follows; NTRK1/2/3-rearranged NSCLC; ROS1-rearranged NSCLC; ALK- or ROS1-rearranged NSCLC; NTRK/1/2/3-rearranged metastatic colorectal cancer (mCRC); ROS1-rearranged mCRC; ALK-rearranged mCRC; NTRK1/2/3-rearranged other solid tumour; ROS1-rearranged other solid tumour; ALK-rearranged other solid tumour. Each participant received 600mg oral entrectinib daily.
Follow-up	Follow up – approximately 24 to 36 months
Primary Outcomes	• Objective Response Rate [Time Frame: Approximately 24 months]
Secondary Outcomes	• Duration of Response [Time Frame: Approximately 24 months] • Time to Response [Time Frame: Approximately 24 months] • Clinical Benefit Rate [Time Frame: Approximately 24 months] • Intracranial Tumour Response [Time Frame: Approximately 24 months] • CNS Progression-free Survival [Time Frame: Approximately 24 months] • Progression-free Survival Time Frame: Approximately 30 months] • Overall Survival [Time Frame: Approximately 36 months]
Key Results	Primary endpoint results have not yet been published, however early case series results have been released on 3 participants (2 with a TPR-NTRK gene fusion, and 1 with an SCL4-ROS1 gene fusion) of this clinical trial which have been treated with 600mg entrectinib daily. These 3 patients showed evidence of clinical improvement, with normalization of the tumour biomarker CA19-9 and confirmed partial responses as per RECIST v1.1 in the 2 patients with a TPR-NTRK fusion, 1 of which was associated with a significant decrease in metabolic activity as assessed by PET/CT scan. The patient with the SCL4-ROS1 fusion had stable disease for at least 6 months. The 3 patients had an improvement to, or maintenance of, a high quality of life while on study. At the time of data cutoff, 1 of the patients with a TPR-NTRK fusion remained on treatment > 1 year.[7]
Adverse effects (AEs)	Entrectinib was well tolerated with mostly grade 1-2 adverse events consisting primarily of arthralgias, myalgias, and fatigue.[7]

Expected reporting date	Study completion date reported as October 2020

ESTIMATED COST and IMPACT

COST

The cost of entrectinib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other

☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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