Innovation Observatory

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EVIDENCE BRIEFING
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Entrectinib for ROS1 fusion positive, locally advanced or metastatic non-small cell lung cancer

NIHRIO ID	24158	**NICE ID**	10016
Developer/Company	Roche Products Ltd	**UKPS ID**	649345

Licensing and market availability plans	Entrectinib is currently in phase II clinical trials for the treatment of ROS-1 fusion positive, locally advanced or metastatic non-small cell lung cancer.

SUMMARY

Entrectinib is in clinical development for the oral treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) with ROS1 genetic rearrangement. NSCLC makes up the majority of lung cancer cases and can be classified according to how far the cancer has spread. Stage III, or locally advanced NSCLC is when the cancer has spread within the lungs and surrounding areas. Stage IV NSCLC is when the cancer has spread to other locations and organs within the body. Many different factors can increase the risk of developing NSCLC, including certain genetic changes, such as changes to the ROS1 gene which lead to increased levels of the ROS1 protein. Increased levels of ROS1 have been found in many different types of cancer, including NSCLC, and are thought to contribute to the development of cancer.

Entrectinib is a drug that specifically targets and blocks the ROS1 protein overproduced in many types of cancers including NSCLC. Preclinical trials suggest it may be more potent in targeting ROS1 than the currently approved therapy crizotinib. If licenced entrectinib would provide an additional specific treatment option for patients with ROS rearranged, locally advanced or metastatic NSCLC.

PROPOSED INDICATION

ROS-1 fusion-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC)[a]

TECHNOLOGY

DESCRIPTION

Entrectinib (RXDX-101) is an oral drug[1] designed to target tumours that harbour gene fusions 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 localised 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 currently being developed for the treatment of ROS-1 fusion positive, locally advanced or metastatic NSCLC. In the phase II clinical trial (STARTRK-2, NCT02568267), oral entrectinib was given to patients with ROS-1 rearranged NSCLC.[6] The proposed dose of entrectinib is 600mg per day taken as 100-200mg oral capsules.[a]

INNOVATION AND/OR ADVANTAGES

If licenced, entrectinib would offer an additional treatment option for patients with ROS1 fusion locally advanced or metastatic NSCLC, the only other licenced product for the targeted treatment of this condition being crizotinib.[7] Additionally, preclinical evidence suggests entrectinib was 30 times more potent than crizotinib against ROS1 and entrectinib also seems to cross the blood brain barrier more efficiently than crizotinib.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Entrectinib does not currently have Marketing Authorisation in the EU/UK for any indication.[9]

Entrectinib is currently in phase II development for the treatment of NTRK-fusion positive, locally advanced or metastatic solid tumours.[6]

[a] Information provided by the company on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Lung cancer is classified into two main histologic types: small-cell lung cancer (SCLC) or non-small-cell lung cancer (NSCLC).[10] NSCLC comprises approximately 87% of lung cancers in the UK. There are three common types of NSCLC; adenocarcinoma (the most common type which starts in the mucus making glands in the lining of the airways), squamous cell cancer (develops of the flat cells that cover the surface of the airways and tends to grow near the centre of the lung), large cell carcinoma (cancer cells which appear large and round under the microscope).[11] NSCLC can be graded to give an idea of how quickly the cancer may grow and whether it is likely to spread. NSCLC is graded from stages 1 to 4,[12] with stage 3 indicating cancer which has spread locally (to the surrounding tissue and lymph nodes)[13] and stage 4 indication cancer which has spread to other areas and organs.[14]

The ROS1 gene encodes for a receptor tyrosine kinase and rearrangement of the ROS1 gene leads to a constitutively activated downstream signalling with oncogenic properties. ROS1 protein rearrangements have been found in many different cancers. ROS1 rearrangement in NSCLC is associated with slight/never smoking patients and adenocarcinoma histology. Identification of ROS1 rearrangement in NSCLC is important as it has therapeutic consequences, as treatment with targeted inhibitors results in significantly better survival when compared to conventional therapy.[15]

Certain factors can increase the risk of developing lung cancer, including; smoking tobacco, exposure to radiation (by exposure to radon gas and previous radiotherapy treatment), exposure to certain chemicals (e.g. asbestos, silica and diesel engine exhaust fumes), previous lung disease (e.g. tuberculosis and COPD), family history of lung cancer and certain genetic mutations and lowered immunity (e.g. due to certain conditions e.g. HIV/AIDS, rheumatoid arthritis and systemic lupus erythematosus, or immunosuppressive medications).[16] Symptoms of lung cancer include a persistent cough (which may be more painful, have a different sound or bring up coloured mucus), shortness of breath, coughing up blood, aches and pains in the chest or shoulder, loss of appetite, weight loss and fatigue.[17]

CLINICAL NEED AND BURDEN OF DISEASE

Lung cancer is the third most common cancer in the UK, accounting for 13% of all new cancer cases in 2015. Age standardised incidence rates of lung cancer in England in 2015 was 76 per 100,000. Approximately 85-95% lung cancer cases in England have a stage recorded at diagnosis. Of these, 72-76% are diagnosed at stage III and IV.[18] In 2012 there were 85, 000 people living in the UK with a lung cancer diagnosis including people living with the condition, those in remission and those who have been cured.[19]

NSCLC comprises of 87% lung cancer cases in the UK[11] and prevalence of ROS rearrangement in NSCLC ranges from 0.5% to 2%.[15]

Net survival rates for the UK in 2014 for males and females with stage III lung cancer was 42% and 46% respectively and for males and females with stage IV lung cancer was 15% and 19% respectively.[20]

In England and Wales in 2017 there were 30,131 deaths with malignant neoplasm of trachea, bronchus and lung (ICD-10 codes C33-34) recorded as the underlying cause.[21]

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Treatment of NSCLC will depend on the stage of the cancer and the general health of the patient. The main treatment options for stage III NSCLC include surgery (only if the cancer can be completely removed), chemotherapy and radiotherapy. Stage IV NSCLC treatment generally includes chemotherapy, immunotherapy, radiotherapy and symptom control management.[22] Patients with ROS1 rearrangement NSCLC may receive these general treatments, however there are some targeted drug treatments which have been found to be particularly effective in those with this specific gene rearrangement and may be given before chemotherapy or immunotherapy.[23]

CURRENT TREATMENT OPTIONS

- Chemotherapy
  - Pemetrexed-platin doublet treatment – shows special activity in ROS1 positive patients[15]
- Targeted therapies:
  - Crizotinib – recommended by NICE for the treatment of advanced ROS1-positive NSCLC (use within the Cancer Drugs Fund)[24]

PLACE OF TECHNOLOGY

If licensed, entrectinib will offer an additional treatment option for patients ROS1 rearrangement locally advanced or metastatic NSCLC, who currently have few targeted treatment options available.

CLINICAL TRIAL INFORMATION

Trial	STARTRK-2, NCT02568267, 2015-003385-84, RXDX-101-02; entrectinib; phase II
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[6]
Location	EU (including UK), USA, and other countries
Design	Non-randomised, open label, parallel assignment, basket trial
Participants	n=300 (planned); aged 18 years or older; NSCLC; locally advanced or metastatic; histologically or cytologically confirmed ROS1 gene rearrangement
Schedule	As part of this basket trial, participants with ROS1 rearranged NSCLC were given oral entrectinib.
Follow-up	Follow-up approximately 36 months
Primary Outcomes	Objective Response Rate [Time Frame: Approximately 24 months] - Assessed by blinded independent central review (BICR) using RECIST v1.1
Secondary Outcomes	• Duration of Response [Time Frame: Approximately 24 months] - Assessed by blinded independent central review (BICR) using RECIST v1.1 • Time to Response [Time Frame: Approximately 24 months] - Assessed by blinded independent central review (BICR) using RECIST v1.1

	• Clinical Benefit Rate [Time Frame: Approximately 24 months] - Assessed by blinded independent central review (BICR) using RECIST v1.1 • Intracranial Tumor Response [Time Frame: Approximately 24 months] - Assessed by blinded independent central review (BICR) using RANO or RANO-BM, as applicable • CNS Progression-free Survival [Time Frame: Approximately 24 months] - Assessed by blinded independent central review (BICR) using RANO or RANO-BM, as applicable • Progression-free Survival [Time Frame: Approximately 30 months] - Assessed by Kaplan-Meier method • Overall Survival [Time Frame: Approximately 36 months] - Assessed by Kaplan-Meier method
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as October 2020

ESTIMATED COST

The cost of entrectinib is not yet known.

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (TA529). July 2018.
- NICE clinical guideline. Lung cancer: diagnosis and management (CG121). April 2011.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.

NHS ENGLAND (POLICY/COMMISSIONING) 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. 2016 Clinical Commissioning Policy: Robotic assisted lung resection for primary lung cancer. 16024/P.
- NHS England. 2013 Clinical Commissioning Policy: Stereotactic Ablative Body Radiotherapy for Non-Small Cell Lung Cancer (Adult). B01/P/a.

OTHER GUIDANCE

- European Society for Medical Oncology. Metastatic non-small cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. 2014.[25]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[26]
- National Comprehensive Cancer Network. The NCCN clinical practice guidelines in oncology. Non-small cell lung cancer. 2013.[27]

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