Health Technology Briefing
September 2024

Entrectinib for treating relapsed or refractory locally advanced or metastatic solid tumours with NTRK1/2/3 gene fusions in children and adults

Company/Developer	Roche Products Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 38607	NICE ID: Not available	UKPS ID: 674562

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Entrectinib is in clinical development for the treatment of children and adolescents with relapsed (recurrent) or refractory (treatment resistant) locally advanced or metastatic solid or primary tumours harbouring neurotropic tropomyosin receptor kinase (NTRK) 1/2/3. Solid tumours are defined as abnormal masses of tissue that usually do not contain cysts or liquid areas and may be benign or 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 and cause an uncontrolled increase of cancer cells. These gene mutations are rare, hence the need for effective therapies that can target gene alterations shared by multiple tumour types regardless of site of origin.

Entrectinib is administered orally and works by blocking the action of the abnormal proteins produced by cancers with NTRK1/2/3 gene fusions. This prevents the uncontrolled increase of cancer cells and slows down cancer growth. If licensed, entrectinib would offer a treatment option for many types of solid tumours that are positive to NTRK gene mutation.

Proposed Indication

Treatment of paediatric patients with relapsed and refractory locally advanced or metastatic solid tumours.[1]

Technology

Description

Entrectinib (RXDX-101; Rozlytrek) is an oral drug designed to target tumours that harbour activating mutations to NTRK 1/2/3 and ROS1.[2,3] Entrectinib is a tyrosine kinase inhibitor which acts on several receptors. It functions as an ATP competitor to inhibit tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, TRKC, as well as proto-oncogene tyrosine-protein kinase ROS1 and anaplastic lymphoma kinase (ALK). TRK receptors produce cell proliferation via downstream signalling through the mitogen activated protein kinase, phosphoinositide 3-kinase, and phospholipase C-γ. Inhibition of these pathways suppresses cancer cell proliferation and shifts the balance in favour of apoptosis resulting in shrinking of tumour volume.[4]

Entrectinib is currently in clinical development for the treatment of locally advanced or metastatic solid or primary central nervous system (CNS) tumours in children and adolescents and/or who have no satisfactory treatment options. In phase I/II dose escalation trial (STARTRK-NG; NCT02650401) and phase II platform trial (TAPISTRY; NCT04589845) entrectinib was administered orally once daily.[1,5,6]

Key Innovation

Entrectinib is a histology-independent or tumour-agnostic treatment.[7,8] 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.[9] Entrectinib can cross the blood–brain barrier, and could thus potentially be effective in the treatment of brain metastases.[9] Entrectinib is generally well tolerated, with a manageable safety profile, and expands the range of treatment options for advanced NTRK+ solid tumours and may be suitable for treating patients with existing CNS metastases and those who are at risk of developing CNS metastases.[10] In trials in adults, entrectinib induced clinically meaningful and durable systemic responses in tyrosine kinase inhibitor (TKI)-naïve patients with locally-advanced or metastatic NTRK+ solid tumours, irrespective of the presence or absence of CNS metastases at baseline.[10] If licensed, entrectinib would offer an effective treatment option for children and adolescents with locally advanced or metastatic solid or primary CNS tumours.

Regulatory & Development Status

Entrectinib currently has Marketing Authorisation in the EU/UK for the following indications:[11]

- treatment of adult and paediatric patients 12 years of age and older with solid tumours expressing a NTRK gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have not received a prior NTRK inhibitor, and who have no satisfactory treatment options
- treatment of adult patients with ROS1 positive, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors

Entrectinib is currently in phase II/III clinical development for the treatment of the following conditions:[12]

- breast cancer
- NSCLC
- cancers of unknown primary site

- high grade glioma
- haematological malignancy
- ROS1 gene fusion-positive cancers

Entrectinib has the following regulatory designations/awards:[13-16]

- a PRIME status for 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 by the EMA in October 2017
- an orphan drug in the USA in 2017 for the treatment of NTRK fusion-positive solid tumours
- a Breakthrough Therapy by the US FDA 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 May 2017
- Priority Review for the treatment of adult and paediatric patients with NTRK fusion-positive, locally advanced or metastatic solid tumours, as well as patients with metastatic ROS1-positive NSCLC in February 2019

Patient Group

Disease Area and Clinical Need

Solid tumours are defined as abnormal masses of tissue that usually do not contain cysts or liquid areas, and may be benign or malignant. Examples of solid tumours are sarcomas, carcinomas, and lymphomas.[17] The family of NTRK is a part of the transmembrane tyrosine kinases responsible for neuronal development. The members of this receptor family are TRKA, TRKB and TRKC and they are encoded by the genes NTRK1, NTRK2 and NTRK3. Alterations of NTRK genes can induce carcinogenesis both in neurogenic and non-neurogenic cells.[18] The prevalence of NTRK fusions in solid tumours is estimated to be 0.3% in adult and paediatric patients. However, it is more common in rare types of solid tumour.[19] Locally advanced cancers are cancers that have spread from where they started to nearby tissue or lymph nodes, while metastatic cancers have spread from where they started to distant parts of the body.[20,21] Refractory cancer refers to cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment.[22] Relapsed cancer means that the disease has returned after a period of remission.[23] 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.[24]

In England, in 2022-2023, there were 12,913 finished consultant episodes (FCEs) for malignant neoplasm without specification of site (ICD-10 code C80) and 8,343 admissions resulting in 44,247 FCE bed days and 4,893 day cases. The prevalence of NTRK gene fusions is uncertain, however, it is estimated to be between 0.25% and 0.31% in adults and between 0.34% and 0.49% in children and young people.[7]

Recommended Treatment Options

National Institute for Health and Care Excellence (NICE) recommend the following treatment options for NTRK fusion-positive solid tumours:[7,25]

- Larotrectinib, in adults and children if the disease is locally advanced or metastatic or surgery could cause severe health problems and they have no satisfactory treatment options

- Entrectinib, in adults and children 12 years and older if the disease is locally advanced or metastatic or surgery could cause severe health problems and they have not had an NTRK inhibitor before and they have no satisfactory treatment options

Clinical Trial Information	
Trial	**STARTRK-NG**, NCT02650401, EudraCT 2019-001155-39; A Phase 1/2, Open-Label, Dose-Escalation And Expansion Study Of Entrectinib (Rxdx-101) In Paediatrics With Locally Advanced Or Metastatic Solid Or Primary CNS tumours And/Or Who Have No Satisfactory Treatment Options **Phase III:** Active, not recruiting **Location(s):** Four EU, UK, USA, Canada and other countries **Primary completion date:** June 2025
Trial Design	Non-randomised, open-label, single group assignment
Population	N=69 (actual); subjects with relapsed or refractory locally advanced or metastatic extracranial solid tumours, primary brain tumours harbouring NTRK1/2/3 or ROS1 gene fusions, and extracranial solid tumours harbouring NTRK1/2/3 or ROS1 gene fusions; aged 0 to 18 years.
Intervention(s)	Entrectinib administered orally once daily[5]
Comparator(s)	No comparator
Outcome(s)	Primary outcome measures: • Maximum tolerated dose [time frame: approximately 6 months] • Recommended phase 2 dose (RP2D) of F1 formulation in paediatric participants able to swallow intact capsules [time frame: approximately 6 months] • RP2D of F06 formulation in paediatric participants able to swallow intact capsules [time frame: approximately 6 months] • RP2D of F06 formulation in paediatric in participants dosed via feeding tube (nasogastric tube or gastric tube) [time frame: approximately 6 months] • RP2D of minitablets/F15 formulation in paediatric participants unable to swallow intact capsules [time frame: approximately 6 months] • Cohort B: objective response rate (ORR) [time frame: approximately 6 months] • Cohort D: ORR [time frame: approximately 6 months] See trial record for full list of other outcomes.
Results (efficacy)	At data cutoff, 43 patients, median age of 7 years, were response evaluable. In patients with fusion-positive tumours, ORR was 57.7% (95% CI 36.9-76.7), median duration of response was not reached, and median (interquartile range) duration of treatment was 10.6 months (4.2-18.4).[5]
Results (safety)	The most common treatment-related adverse event was weight gain (48.8%). Nine patients experienced bone fractures (20.9%).[5]

Trial	**TAPISTRY,** NCT04589845, EudraCT 2020-001847-16; Tumour-Agnostic Precision Immuno-Oncology and Somatic Targeting Rational for You Platform Study **Phase II:** Active, Recruiting **Locations:** 9 EU, UK, USA, Canada and other countries. **Primary completion date:** September 2032
Trial Design	Non-randomised, open-label, parallel assignment
Population	N=920 (estimated); child, adult, and older adult patients with unresectable, locally advanced or metastatic solid tumours determined to harbour specific oncogenic genomic alterations or who are tumour mutational burden-high as identified by a validated next-generation sequencing assay
Intervention(s)	• Entrectinib administered orally once daily in repeated 28-day cycles at a dose of 600 mg/day • Alectinib administered orally twice daily with food at a dosage of 600 mg in repeated 28-day cycles • Atezolizumab administered by intravenous (IV) infusion at a fixed dose of 1200 mg on day 1 of each 21-day cycle • Ipatasertib administered orally once daily at the starting dose of 400 mg in repeated 28-day cycles • Trastuzumab emtansine administered by IV infusion at 3.6 mg/kg every 21 days • Idasanutlin administered orally at 250 mg once daily for days 1-5 of each 28-day cycle • Inavolisib administered orally once daily at a starting dose of 9 mg in repeated 28-day cycles • Belvarafenib administered orally at a dose 400 mg twice daily for 4 weeks • Pralsetinib administered orally on a continuous daily dosing regimen at a dose of 400 mg/day for 4 weeks • GDC-6036 administered orally on a continuous daily dosing regimen for 3 weeks • Camonsertib administered orally on days 1-3 and days 8-10 of every 21-day cycle
Comparator(s)	No comparator
Outcome(s)	Primary outcome measure: • All cohorts: Independent Review Committee -assessed objective response rate based on confirmed objective response per response evaluation criteria in solid tumours, version 1.1 (RECIST v1.1) [time frame: approximately up to 12 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Entrectinib is already marketed in the UK;[26]

- a pack of 90 x 200mg capsules costs £5,160
- a pack of 30 x 100mg capsules costs £860

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Entrectinib for treating NTRK fusion-positive solid tumours (TA644). August 2020.
- NICE technology appraisal. Larotrectinib for treating NTRK fusion-positive solid tumours (TA630). May 2020.
- NICE guideline. Suspected cancer: recognition and referral (NG12). October 2023.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for NHS Standard Service Specification Template for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B15/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- Wales Cancer Network. NTRK Gene Fusion Testing Clinical Guidance v3.0. 2023.[27]

Additional Information

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