Investigational entrectinib: What you need to know

What is entrectinib?

Entrectinib (RXDX-101) is an investigational, next generation oral medicine in development for the treatment of locally advanced or metastatic solid tumours that harbour ROS1 or NTRK 1/2/3 fusions. It is a potent, selective central nervous system (CNS)-active tyrosine kinase inhibitor (TKI) currently under investigation in a phase II basket study to assess whether it could be an effective treatment for shrinking tumours across a broad range of cancers harbouring ROS1 or NTRK positive gene fusions.[1,2] It is a once-daily treatment that, if approved, can help patients regain quality of life through its targeted mode of action.

What are ROS1 and NTRK gene fusions?

ROS1 and NTRK gene fusions are a specific type of mutation which can cause signalling malfunctions. These malfunctions cause cells to grow and proliferate in an uncontrolled manner, resulting in cancer.[2] These cancers can occur at various sites of the body, with ROS1 occurring in non-small cell lung cancer (NSCLC) and NTRK occurring in many locations, including NSCLC, colorectal cancer, salivary gland cancer, papillary thyroid cancer, melanoma, and sarcoma.[1] ROS1 gene fusions occur in 1-2% of NSCLC, while NTRK gene fusions have been identified in more than 30 different solid tumour types, many of which are rare.[3,4]

Fast Facts

- **Entrectinib targets ROS1 and NTRK** in a range of tumours, allowing for a truly personalised approach to patient care.[1,2]
- **Entrectinib is active in the CNS, enabling it to treat CNS metastases.**[1,2] More than 30% of patients with NSCLC will develop brain metastases during the course of their disease, which can lead to debilitating symptoms including memory loss, seizures and changes in behaviour and personality, and is an important unmet need.[5,6]
- **Entrectinib shrank tumours in 77.4% (objective response rate; ORR) of people with locally advanced or metastatic ROS1-positive NSCLC** in an integrated analysis of the pivotal phase II STARTRK-2, phase I STARTRK-1 and phase I ALKA trials.[7] Importantly, results showed that **entrectinib shrank tumours in more than half of people with cancer in the CNS** (intracranial ORR: 55.0%).[7]

How does entrectinib work?

Entrectinib is designed to inhibit kinase activity of the TRK A/B/C and ROS1 proteins, whose activating fusions cause cells to grow and proliferate in certain rare cancer populations.[1,2] Importantly, entrectinib can cross the blood-brain barrier (BBB), a semi-permeable membrane that controls the entry of cells and molecules to the brain and central nervous system.[1,2,8] This means that entrectinib can target tumours that have metastasised to the CNS, a common site of progression in ROS1- gene fusion positive NSCLC patients. Currently, there are limited effective non-invasive therapeutic options for patients with these gene fusions. Comprehensive genomic profiling is required to identify individuals most likely to benefit from tumour-agnostic entrectinib.

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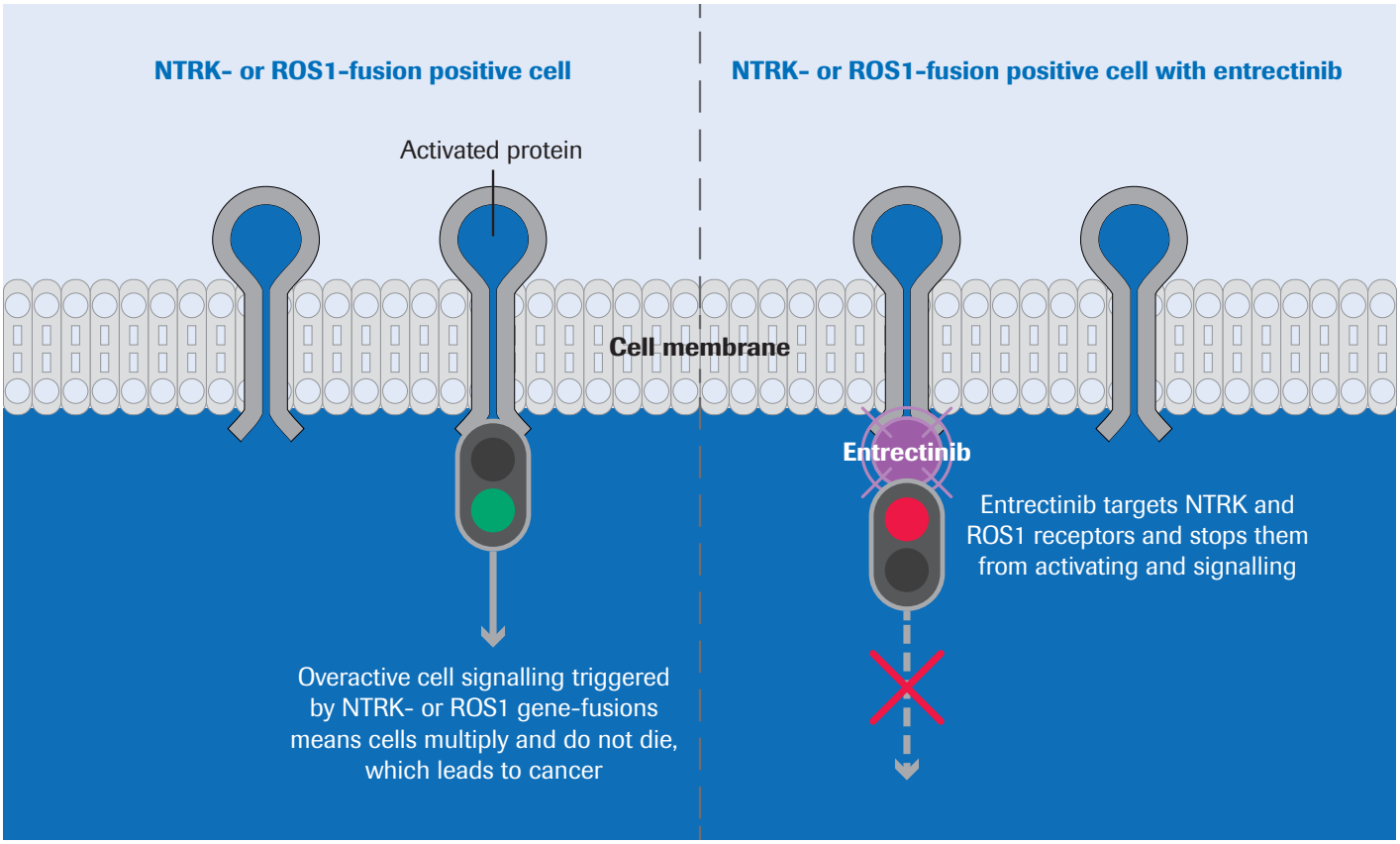

Figure 1: How entrectinib works in NTRK and ROS1 fusion-positive cells

What is the latest clinical evidence for entrectinib?

In an integrated analysis of three studies, including the global phase II STARTRK-2 basket study, the results showed that in people with locally advanced or metastatic ROS1 fusion-positive NSCLC, entrectinib shrank tumours (objective response rate; ORR) in 77.4% people with ROS1-positive NSCLC.[7] In addition, duration of response to entrectinib reached a median of 24.6 months (duration of response; DOR).[7] Importantly, entrectinib was shown to reduce tumours in people with cancer in the central nervous system (CNS) (intracranial ORR: 55%).[7] The safety profile of entrectinib was consistent with that seen in previous analyses, and no new safety signals were identified.[7]

What is the clinical significance of entrectinib?

Since entrectinib targets ROS1-fusion positive NSCLC and NTRK gene fusion positive tumours across a range of rare cancers (i.e. tumour agnostic) and also impacts CNS metastases, once approved, it can provide an additional treatment option for patients with few options. Many patients on the standard treatment for ROS1 gene fusion tumours with CNS disease at the time of diagnosis relapse within one year of starting therapy.[9] There is also a high unmet need for effective, safe and well tolerated treatments for people who have tumours which have spread to the CNS; more than 30% of individuals with ROS1 fusion-positive NSCLC have CNS metastases.[9]

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What is the value of this latest entrectinib data for Roche?

Entrectinib is the latest breakthrough in Roche's oncology portfolio of targeted medicines aimed at advancing the personalisation of cancer treatment. This innovation brings together cutting-edge technology, precision medicine, and genomic profiling, paving the way even further to personalised approaches to healthcare, and reinforcing Roche's position as a leading innovator in precision medicine. Entrectinib has been granted Breakthrough Therapy Designation (BTD) by the US FDA; Priority Medicines (PRIME) designation by the EMA; and the Sakigake designation by the Japanese health authorities.[10]

References

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