Entrectinib: A review in NTRK+ solid tumours and ROS1+ NSCLC

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Video Abstract

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Abstract

NTRK, ROS1, and ALK gene fusions are recognised oncogenes in many cancers. Oncogenic fusions result in constitutively active tyrosine kinases and downstream activation of pathways associated with tumour growth, survival, and proliferation. NTRK fusions, for example, are found in both adult and paediatric cancers and are extremely common in some rare cancers. All three fusion types are found in non-small cell lung cancer. At diagnosis, many patients with NTRK-fusion-positive solid tumours, including NTRK-positive non-small cell lung cancer, or with ROS1-positive non-small cell lung cancer also have brain metastases. These metastases are linked to a worse prognosis. Although effective drugs exist for both NTRK-positive solid tumours and ROS1-positive non-small cell lung cancer, most don't penetrate the CNS well enough to treat brain metastases. Entrectinib, an orally active small-molecule tyrosine kinase inhibitor that selectively inhibits TRK, ROS1 and ALK, acts in both the periphery and the CNS. Unlike other similar tyrosine kinase inhibitors, entrectinib is a weak P-glycoprotein substrate, which improves its CNS retention. Entrectinib's main metabolite is also active, equally potent, and able to penetrate the CNS. Entrectinib is currently approved in several countries for the treatment of NTRK-positive solid tumours in patients aged 12 years and older and ROS1-positive non-small cell lung cancer in adults. According to pooled data from three clinical trials, entrectinib can produce clinically meaningful and durable effects in adults with locally advanced or metastatic forms of these diseases, even those with CNS involvement. The primary outcomes in these trials were the systemic objective response rate, or ORR, and the duration of response, or DoR. For both cancer types, over 60% of patients achieved a systemic objective response, with a median duration of response of more than a year. For both cancer types, the systemic objective response rate did not differ between patients with or without CNS metastases at baseline. However, the median duration of response, progression-free survival, and overall survival were shorter in patients with CNS metastases at baseline, reflecting the worse prognosis in these patients. Among patients with CNS metastases at baseline, approximately half achieved an intracranial objective response, with a median intracranial duration of response of 8 months for NTRK-positive solid tumours and over one year for ROS1-positive non-small cell lung cancer. Based on extrapolated adult data from the three trials and data from another ongoing study, entrectinib is also anticipated to be effective in paediatric patients with NTRK-positive solid tumours. The drug was generally well tolerated in these four clinical trials. The most common adverse reactions were fatigue, constipation, taste distortion, oedema, dizziness, diarrhoea, and nausea. Overall, the data suggest that entrectinib helps fill an unmet clinical need: it's effective against these two gene fusion-driven cancers systemically and in the CNS. Entrectinib thus expands the range of treatment options for patients with NTRK-positive solid tumours or with ROS1-positive non-small cell lung cancer. Furthermore, it's particularly promising for patients with these cancers who have, or are at risk of developing, brain metastases.