NEW DRUGS

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Entrectinib

Approved indications: non-small cell lung cancer and solid tumours

Rozlytrek (Roche)
100 mg and 200 mg hard capsules

Like crizotinib, entrectinib is an oral tyrosine kinase inhibitor for non-small cell lung cancer. It inhibits the proto-oncogene tyrosine-protein kinase ROS1, tropomyosin receptor kinases (TRK) and anaplastic lymphoma kinase (ALK). These kinases are associated with unconstrained cell proliferation so inhibiting them aims to slow tumour growth. Unlike crizotinib, entrectinib can cross the blood–brain barrier and so has activity at intracranial sites.

Entrectinib is specifically indicated for:

- adults with ROS1-positive advanced non-small cell lung cancer
- adults and children over 12 years with metastatic or inoperable solid tumours, with a neurotrophic tyrosine kinase (NTRK) gene fusion, that have progressed after treatment or have no alternative therapy (provisional approval only).

The approval of entrectinib for both indications is based on prospective subgroup analyses of three phase I–II, single-arm, open-label trials called ALKA, STARTRK-1 and STARTRK-2. These studies enrolled patients with solid tumours (e.g. sarcoma, non-small cell lung cancer, breast). In a pooled analysis of participants with ROS1-positive advanced non-small cell lung cancer, 77% (41/53) responded to once-daily entrectinib (100–1600 mg) – three had a complete response and 38 had a partial response. Overall, the median duration of response was 24.6 months and median progression-free survival was 19 months. In a subgroup of 23 patients who had central nervous system metastases at baseline, 17 had a partial response.[1]

In a pooled analysis of participants with NTRK-positive tumours, 57% (31/54) responded to entrectinib 600 mg once a day – four had a complete response and 27 had a partial response. The median duration of response was 10 months. In a subgroup of 12 patients who had central nervous system disease at baseline, six had a partial response.[2]

In a safety cohort of 355 patients, the most common grade 3 or 4 adverse events included lung infection (5%), weight gain (7%), dyspnoea (6%), fatigue (5%), cognitive disorders (4.5%), syncope (2.5%), pulmonary embolism (3.4%), hypoxia (3.4%), pleural effusion (3.1%), hypotension (2.8%), sepsis (2.5%), diarrhoea (2%) and urinary tract infection (2.5%). In terms of grade 3 or 4 laboratory abnormalities, the most common were lymphopenia (12%), hyperuricaemia (10%), increased lipase (10%), anaemia (9%), neutropenia (7%), hypophosphataemia (7%) and increased amylase (5.4%). Dose interruptions because of an adverse event occurred in 46% of patients and 9% of patients discontinued treatment because of an event.

The recommended dose of entrectinib is 600 mg once a day. A reduced dose is recommended for paediatric patients depending on their body surface area. Capsules can be taken with or without food. Maximum plasma concentrations are reached 4–6 hours after administration and most of the dose is excreted in the faeces. Lowering the dose or permanently discontinuing entrectinib is recommended for certain adverse events depending on their severity. These include congestive heart failure, central nervous system effects, hepatotoxicity, hyperuricaemia, prolonged QT interval, anaemia or neutropenia and vision disorders.

Dose adjustment is not likely to be required in renal impairment as elimination via the kidneys is negligible. It is also not required in hepatic dysfunction, although patients with severe impairment have not been studied.

Entrectinib is mainly metabolised by cytochrome P450 (CYP) 3A4. Concomitant use of strong or moderate inhibitors of this enzyme (e.g. cannabidiol) can increase entrectinib exposure and are not recommended. If they cannot be avoided, the entrectinib dose should be reduced. CYP3A4 inducers (e.g. rifampicin) should also be avoided as concomitant use can decrease entrectinib concentrations. Drugs that increase gastric pH (e.g. lansoprazole) can also have this effect.

Entrectinib can increase the concentrations of other drugs that are substrates of CYP enzymes (e.g. midazolam) or P-glycoprotein (e.g. digoxin). Medicines that prolong the QT interval are not recommended with entrectinib.

The majority of patients with ROS1- or NTRK-positive tumours seemed to respond to entrectinib. However, it is difficult to quantify this benefit as patient numbers in the trial were low, particularly the paediatric population, and there were no comparators. Overall survival with entrectinib therapy is currently unknown.

Entrectinib is subsidised on the Pharmaceutical Benefits Scheme for patients with ROS1-positive non-small cell lung cancer who have not previously received crizotinib or could not tolerate it.[3] It is important to note that the approval of entrectinib for patients with NTRK-positive tumours is provisional until the Therapeutic Goods Administration receives more data from the sponsor.

T manufacturer provided the product information

The new drug commentaries in *Australian Prescriber* are prepared by the Editorial Executive Committee. Some of the views expressed on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

REFERENCES

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA.