Larotrectinib

Aust Prescr 2022;45:99
https://doi.org/10.18773/austprescr.2022.035

Approved indication: solid tumours

Vitrakvi (Bayer)
25 mg and 100 mg capsules
oral solution containing 20 mg/mL

Genomic research has found that in some rare cases apparently different cancers can share the same genetic abnormality. An example involves the genes that encode for the tropomyosin receptor kinases TRKA, TRKB and TRKC. Rearrangement of these genes results in gene fusion and the production of TRK fusion proteins. These abnormal proteins stimulate cell proliferation which can become cancerous. Inhibition of these effects may therefore be an approach to treating TRK fusion cancers. While these gene fusions have been found in cases of colorectal, lung and thyroid cancer, they are uncommon. They are more frequently found in rare cancers such as infantile fibrosarcoma and congenital mesoblastic nephroma.

Larotrectinib is a selective inhibitor of TRKA, TRKB and TRKC. In animal studies it significantly reduced tumour growth.

The drug is taken by mouth twice a day. A steady state is reached in about a week. Larotrectinib is thought to be metabolised by cytochrome P450 (CYP) 3A4/5, but about 30% of the dose is excreted unchanged in the urine. Although no adjustment is required in renal disease, the dose needs to be reduced if there is moderate or severe liver impairment. Adjustments are also needed if strong inhibitors or inducers of CYP3A4 cannot be avoided.

Conducting randomised trials in rare diseases is difficult and, in the case of TRK fusion cancers, there is more than one type of tumour to study. The approval of larotrectinib is therefore mainly based on three open-label phase I and phase II trials.[1] These trials enrolled a total of 159 patients, ranging from babies to someone 84 years old. Most had already received standard therapy for locally advanced or metastatic tumours including soft tissue sarcoma, non-small cell lung cancer and thyroid cancer. Treatment with larotrectinib ranged from a day to over 47 months. In a pooled analysis 79% (121/153) of the patients had an objective response, such as a reduction in tumour size. There was a complete response in 16% of the patients. Overall, the median duration of the response was 35.2 months. The median overall survival was 44.4 months.[1]

Only two patients discontinued larotrectinib because of adverse effects, although 8% (13/159) required a dose reduction. Adverse events were similar in adults and children. They included fatigue, myalgia, constipation, nausea and vomiting. Some patients experience neurological symptoms, such as dizziness, particularly at the start of treatment. Liver function should be monitored as aminotransferase concentrations can increase. Some patients develop anaemia.[1]

Long-term safety is currently unclear. There is a potential for the tumours to develop resistance to larotrectinib.

In view of the rarity of TRK fusion cancers, there are limited data about the efficacy, safety and outcomes for larotrectinib. It is therefore appropriate that larotrectinib has only been provisionally approved for when no alternatives are available to treat advanced or metastatic solid tumours, or when surgery is likely to cause severe morbidity in patients with TRK fusion cancers.

T manufacturer provided the AusPAR and the product information

REFERENCE

1. Hong DS, DuBois SG, Kummar S, Farago AF, Albert CM, Rohrberg KS, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020;21:531-40. https://doi.org/10.1016/s1470-2045(19)30856-3

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 websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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.