NEW DRUGS

Zanubrutinib

Approved indications: mantle cell lymphoma, Waldenström's macroglobulinaemia

Brukinsa (BeiGene)
80 mg capsules

Zanubrutinib is an inhibitor of Bruton's tyrosine kinase. This kinase is involved in amplifying the signals from B-cell receptors. It is essential for B-cell maturation and proliferation. Bruton's tyrosine kinase is therefore a target for the treatment of cancers that involve B cells for example non-Hodgkin lymphomas, including Waldenström's macroglobulinaemia and mantle cell lymphoma. Like the previously approved ibrutinib and acalabrutinib, zanubrutinib irreversibly binds to the kinase resulting in a prolonged inhibition of its activity.

The capsules are taken once or twice a day. Food has no effect on absorption. Zanubrutinib has a half-life of two to four hours with most of the dose being metabolised. As this metabolism involves cytochrome P450 (CYP) 3A, zanubrutinib will interact with inhibitors of this enzyme such as the azole antifungals, erythromycin and grapefruit juice. Inducers of CYP3A, such as rifampicin, phenytoin and St John's wort, should be avoided. A reduced dose of zanubrutinib is recommended for patients with severe hepatic impairment.

The efficacy and safety of zanubrutinib in mantle cell lymphoma was investigated in a phase II open-label trial. All 86 patients in the trial had been previously treated, but the lymphoma was refractory or had relapsed. They were all given zanubrutinib 160 mg twice daily. After a median follow-up of 18.4 months there had been an objective response, according to the international criteria for assessing lymphomas, in 72 (84%) of the patients. There was a complete response in 59 (68.6%). The estimated median duration of the response was 19.5 months with a median progression-free survival of 22.1 months. Overall survival at 12 months was 84.1%.[1]

Following a favourable response in preliminary studies of zanubrutinib in Waldenström's macroglobulinaemia, an open-label phase III trial enrolled 201 patients who were unsuitable for immunochemotherapy or had relapsed or refractory disease. They were randomised to receive zanubrutinib 160 mg twice daily (102 patients) or ibrutinib 420 mg once daily (99 patients). The response to treatment was assessed by an independent review committee using international consensus criteria. After a median follow-up of 19.4 months no patients had achieved a complete response. In the zanubrutinib group 28% were judged to have had a 'very good partial response' compared with 19% of the ibrutinib group. After 18 months, 97% of the zanubrutinib group and 93% of the ibrutinib group were still alive. The median duration of response and median progression-free survival had not been reached when the results were published.[2]

A three-year follow-up of 77 patients with Waldenström's macroglobulinaemia, who had participated in a preliminary study of zanubrutinib, reported an overall response rate of 45.2%. The estimated progression-free survival rate was 80.5% and overall survival was 84.8%.[3]

Pooled safety data from 779 patients showed that the most common adverse reactions include neutropenia, thrombocytopenia, anaemia, haemorrhage, pneumonia and diarrhoea. Some of these reactions were fatal. The dose regimen of zanubrutinib needs to be modified if haematological toxicity occurs. Some patients will develop atrial fibrillation, so particular caution is needed in patients with hypertension or other cardiovascular risk factors. Monitor for signs and symptoms of atrial fibrillation or flutter. During treatment with zanubrutinib secondary cancers can emerge. These are mostly skin cancers so sun protection is important. Overall, 3.6% of the trial participants withdrew because of adverse effects.

Like many new anticancer drugs, the optimum use of zanubrutinib still needs to be determined. It is not yet clear that favourable response rates will lead to improved survival. While more patients with Waldenström's macroglobulinaemia responded to zanubrutinib, the difference from ibrutinib was not statistically significant (risk difference 10.2%, 95% confidence interval –1.5, 22.0). Adverse effects such as atrial fibrillation, hypertension and diarrhoea were more frequent with ibrutinib, but zanubrutinib caused more cases of neutropenia including febrile neutropenia.[2]

T manufacturer provided the product information

REFERENCES

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3. Trotman J, Opat S, Gottlieb D, et al. Zanubrutinib for the treatment of patients with Waldenström macroglobulinemia: 3 years of follow-up. Blood 2020;136:2027-37. https://doi.org/10.1182/blood.2020006449 [Erratum in: Blood 2021;137:1131]

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Some of the views expressed in the following notes 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.

NEW DRUGS

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.