The Medical Letter®

on Drugs and Therapeutics

Volume 65 Published online February 20, 2023

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IN BRIEF

Zanubrutinib *(Brukinsa)* for CLL or SLL

The Bruton's tyrosine kinase (BTK) inhibitor zanubrutinib *(Brukinsa)*, which was previously approved by the FDA for treatment of mantle cell lymphoma, Waldenström's macroglobulinemia, and relapsed or refractory marginal zone lymphoma, has now been approved for treatment of chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) in adults. The BTK inhibitors ibrutinib *(Imbruvica)* and acalabrutinib *(Calquence)* were approved earlier for treatment of CLL and SLL.

BTK INHIBITORS — Ibrutinib has been associated with serious severe adverse effects, particularly atrial fibrillation, infection, rash, and bleeding, that may be related to inhibition of kinases other than BTK. Acalabrutinib and zanubrutinib are more selective BTK inhibitors, which might reduce the risk of these adverse effects.

CLINICAL STUDIES — FDA approval of zanubrutinib for the new indications was based on the results of two randomized trials, one in treatment naive patients with CLL/SLL (SEQUOIA) and one in patients with relapsed or refractory CLL/SLL (ALPINE).

In SEQUOIA, 479 patients without a del(17), a deletion of the short arm of chromosome 17, were randomized to receive zanubrutinib 160 mg twice daily until disease progression or unacceptable toxicity occurred or bendamustine/rituximab intravenously for 6 cycles. At a median follow-up of 26.2 months, median progression-free survival (PFS) was not yet reached in either group. Disease progression occurred in 11% of patients in the zanubrutinib group and in 25% of those in the bendamustine/rituximab group, a statistically significant difference. The overall response rate (ORR) was 93% with zanubrutinib and 85% with bendamustine/rituximab.[1] In 110 patients in the SEQUOIA trial with a 17p deletion who received zanubrutinib, the ORR was 94.5%, the estimated 18-month PFS rate was 88.6%, and the estimated 18-month overall survival (OS) rate was 95.1%.[2]

In ALPINE, 652 patients who received ≥1 previous line of therapy were randomized to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily. At 24 months, the PFS rate was 78.4% in the zanubrutinib group and 65.9% in the ibrutinib group. The ORR was 80% with zanubrutinib and 73% with ibrutinib and more patients in the zanubrutinib group achieved a complete response. The median duration of response was not reached in either arm after a median follow-up of 14.1 months. Among those with a 17p deletion, PFS was longer with zanubrutinib than with ibrutinib. Cardiac adverse effects occurred less often with zanubrutinib than with ibrutinib.[3]

ADVERSE EFFECTS — Decreases in neutrophils, lymphocytes, and platelets have been reported with zanubrutinib; complete blood counts should be monitored during treatment. Fatal and opportunistic infections can occur. Serious hemorrhage, arrhythmias, and secondary primary malignancies have occurred with use of BTK inhibitors.

DRUG INTERACTIONS — Zanubrutinib is a substrate of CYP3A; coadministration with strong or moderate CYP3A inducers should be avoided. If concurrent administration of a moderate CYP3A inducer is necessary, the dosage of zanubrutinib should be increased to 320 mg twice daily. The dosage of zanubrutinib should be reduced to 80 mg once daily when taken with a strong CYP3A inhibitor and to 80 mg twice daily when taken with a moderate CYP3A inhibitor.[4]

PREGNANCY AND LACTATION — Administration of zanubrutinib to pregnant rats during organogenesis was associated with fetal malformations and embryofetal mortality. Females of reproductive potential should be screened for pregnancy before starting zanubrutinib; they should use an effective nonhormonal contraceptive method while taking the drug and for 1 week after the last dose. No data are available on the effects of zanubrutinib on the breastfed infant or milk production. Women should not breastfeed during treatment with zanubrutinib and for one week after the last dose.

DOSAGE, ADMINISTRATION, AND COST — Zanubrutinib is available in 80-mg capsules. The recommended dosage for all indications is 160 mg twice daily or 320 mg once daily. The capsules should be swallowed whole with water. The dosage should be reduced to 80 mg twice daily in patients with severe hepatic impairment. The label specifies a number of dosage adjustments that should be made if adverse effects occur. A 30-day supply of *Brukinsa* costs $13,997.[5] ■

1. CS Tam et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. Lancet Oncol 2022; 23:1031.
2. CS Tam et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. Haematologica 2020; 106:2354.
3. JR Brown et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med 2023; 388:319.
4. Inhibitors and inducers of CYP enzymes, P-glycoprotein, and other transporters. Med Lett Drugs Ther 2023 January 25 (epub). Available at: medicalletter.org/downloads/CYP_PGP_Tables.pdf.
5. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. February 5, 2023. Reprinted with permission by First Databank, Inc. All rights reserved. ©2023. www.fdbhealth.com/drug-pricing-policy.

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 ISSN 1523-2859