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Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Zanubrutinib: A Novel BTK Inhibitor in Chronic Lymphocytic Leukemia and Non-Hodgkin Lymphoma

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H&O What type of drug is zanubrutinib?

CT Zanubrutinib, also known as BGB-3111, is a next-generation Bruton's tyrosine kinase (BTK) inhibitor. It inhibits BTK irreversibly at the cysteine residue 481. Ibrutinib (Imbruvica, Pharmacyclics/Janssen), the first-in-class BTK inhibitor, also binds to this cysteine.

H&O How does zanubrutinib differ from ibrutinib in pharmacokinetics and target occupancy?

CT Zanubrutinib has a more-specific target binding profile than ibrutinib. It binds to BTK at least as potently as ibrutinib. Zanubrutinib has fewer off-target effects on related enzymes, including the epidermal growth factor receptor (EGFR), interleukin 2–inducible T-cell kinase (ITK), Janus kinase 3 (JAK3), human epidermal growth factor receptor 2 (HER2), and tyrosine kinase expressed in hematopoietic carcinoma (TEC). There is the potential that zanubrutinib can hit BTK with fewer off-target side effects. For example, it is thought that the rash and diarrhea sometimes seen with ibrutinib may be related to EGFR blockade. Ibrutinib may not combine well with monoclonal antibodies, such as rituximab (Rituxan, Genentech/Biogen), because of ITK effects on the immune effector cells. Zanubrutinib has the potential to target BTK with fewer off-target side effects, and it may combine better with monoclonal antibodies.

> At the current clinical dose of 160 mg twice daily, zanubrutinib achieves drug exposures that are approximately 6 to 10 times higher than those seen with full-dose ibrutinib.

Studies of pharmacokinetics in animal models and humans have shown that zanubrutinib is well-absorbed. At the current clinical dose of 160 mg twice daily, zanubrutinib achieves drug exposures that are approximately 6 to 10 times higher than those seen with full-dose ibrutinib.

My colleagues and I performed a phase 1 study of zanubrutinib. Enrolled patients underwent lymph node biopsies, which showed continuous BTK occupancy at the tissue sites. This observation is important because it is easy to saturate BTK in the blood, but not at the tissue site. It is known that ibrutinib achieves good BTK saturation in the blood, but there are limited data regarding whether it also saturates the tissue sites affected.

This phase 1 study is still ongoing. Preliminary data have been presented separately for patients with chronic lymphocytic leukemia (CLL), Waldenström macroglobulinemia, and other lymphoma histologies.

H&O How did zanubrutinib perform in the patients with CLL?

CT Early results from our phase 1 trial were presented at the 2017 International Conference on Malignant Lymphoma (ICML). The analysis included data for 69 patients with CLL who were treated in the dose-escalation or dose-expansion phases of the study. Most patients in the study had relapsed/refractory disease. In the dose-escalation phase, the daily doses ranged from 40 mg to 320 mg daily. In the dose-expansion phase, patients received treatment with either 160 mg twice daily or 320 mg once daily.

The adverse events were fairly minor. Approximately half of patients developed some degree of minor bruising or bleeding, as would be expected for a BTK inhibitor. The rate of atrial fibrillation was 1%, which is lower than expected for ibrutinib.

Across the total population of patients with CLL, the response rate was 94%. However, nearly all of the responses were partial; the complete remission rate was only 3% at a median follow-up of only 10 months. This delayed achievement of complete response is characteristic of BTK inhibitors—at early follow-up, the complete response rates tend to be low. Progression-free survival was 100% at 12 months and projected to be approximately 95% at 24 months. An ongoing phase 3 study is comparing the frontline use of single-agent zanubrutinib vs bendamustine (Treanda, Teva) plus rituximab in patients with CLL.

H&O What were the data for zanubrutinib in Waldenström macroglobulinemia?

CT Data from the phase 1 trial for patients with Waldenström macroglobulinemia were updated at the 2017 ICML meeting. Among the 48 evaluable patients, 38 had relapsed/refractory disease. In the dose-escalation phase, the daily doses ranged from 40 mg to 320 mg. In the dose-expansion phase, patients received either 160 mg twice daily or 320 mg once daily.

As with the experience in CLL, the adverse event profile was fairly benign. The most encouraging observation was a very high response rate of 90% overall, at a median follow-up of 12.3 months. The very good partial response (VGPR) rate was also high, at 43%. In comparison, the VGPR for ibrutinib in similar populations is approximately 15%. Based on these promising results, a phase 3 study is comparing zanubrutinib against ibrutinib head-to-head in Waldenström macroglobulinemia. The study has completed enrollment.

H&O What were the data for zanubrutinib in other lymphoma patients?

CT Data for 99 patients with other lymphoma histologies were presented at the 2017 American Society of Hematology (ASH) annual meeting. There were 34 patients with indolent lymphoma, either follicular lymphoma (n=24) or marginal zone lymphoma (n=10). Sixty-five patients had more aggressive lymphoma, either mantle cell lymphoma (n=38) or diffuse large B-cell lymphoma (n=27). All patients had relapsed/refractory disease (with the exception of 1 patient with mantle cell lymphoma).

Among patients with mantle cell lymphoma, zanubrutinib was associated with a high response rate of 88%, and a complete remission rate of 25%. These results are similar to those seen with ibrutinib. For diffuse large B-cell lymphoma, the response rate was 31%. In follicular lymphoma, the overall response rate was 41%, and the complete response rate was 18%, rates that are slightly higher than those seen with ibrutinib. In marginal zone lymphoma, the response rate was high, at 78%.

H&O Are there data for zanubrutinib in combination with other therapies?

CT My colleagues and I evaluated zanubrutinib plus obinutuzumab in a phase 1b trial of patients with CLL/small lymphocytic leukemia or follicular lymphoma. Results were presented at the 2017 ICML conference and updated at the 2017 ASH meeting. There was a very high response rate for patients with follicular lymphoma, with an overall response rate of 76% and a complete remission rate of 38%. These encouraging data led to the launch of a phase 2 study evaluating the combination in patients with follicular lymphoma.

Among the cohort of patients with CLL/small lymphocytic leukemia, the overall response rates were 95% for those with treatment-naive disease and 92% for those with relapsed/refractory disease. The complete response rates were 35% and 20%, respectively.

H&O In general, how do the responses seen with zanubrutinib compare with ibrutinib?

CT The biggest signal comes from Waldenström macroglobulinemia, where the VGPR rate is substantially higher than expected for ibrutinib. It appears that the deeper BTK inhibition may have improved clinical results. The data were sufficiently exciting that we have launched a phase 3 study in this setting, comparing zanubrutinib vs ibrutinib.

H&O How does the safety profile compare with that of ibrutinib?

CT It is hard to comment on safety without results from

phase 3 trials. In general, the safety profile looks no worse than ibrutinib. Rates of atrial fibrillation are typically 5% to 10% with ibrutinib. So far, these rates are approximately 2% to 3% for zanubrutinib.

H&O Does it appear that zanubrutinib can work synergistically in combination with other agents?

CT Animal models suggest that the addition of an anti-CD20 antibody improves the efficacy of zanubrutinib but not ibrutinib. Therefore, according to animal models, zanubrutinib may be a better partner for monoclonal antibodies than ibrutinib. This suggestion has been validated in follicular lymphoma, where there seems to be a very high response rate with zanubrutinib combined with obinutuzumab compared with ibrutinib or zanubrutinib alone.

H&O What is next for zanubrutinib?

CT Currently, there are registration studies in CLL and Waldenström macroglobulinemia. There may be another one in mantle cell lymphoma. The goal is for the US Food and Drug Administration to approve zanubrutinib as a monotherapy first, and then perhaps in combination with a monoclonal antibody or a drug from another class.

Disclosure

Dr Tam has received honoraria and research funding from BeiGene.

Suggested Readings

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