Zanubrutinib: BTK Inhibitor Demonstrates Superior Efficacy in Frontline CLL

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are essentially the same disease, separated only by location. Historically, both diseases have been treated with chemotherapy. In 2016, the US Food and Drug Administration approved ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, for first-line therapy with or without anti-CD20 monoclonal antibodies in patients with CLL.

The approval was based on pivotal phase 3 trials that showed ibrutinib-based therapies yielded better outcomes versus standard chemoimmunotherapy regimens, including progression-free survival (PFS) and overall survival (OS) in one comparison. However, ibrutinib has been associated with side effects, including bleeding, hypertension, arthralgia, diarrhea, and cardiac arrhythmias (both atrial fibrillation and flutter), as well as rare cases of lethal ventricular arrhythmias in trials.

Following ibrutinib, acalabrutinib showed improved outcomes versus chemoimmunotherapy with or without obinutuzumab, an anti-CD20 antibody. Acalabrutinib-based therapies had similar risks as ibrutinib but reduced cardiac toxicities. More recently, venetoclax, a B-cell lymphoma-2 inhibitor, plus obinutuzumab also showed superior efficacy versus chemoimmunotherapy. Despite these advancements in targeted therapies, toxicity remains a concern in patients with CLL, and novel treatment options are needed.

Zanubrutinib, Next-Generation BTK Inhibitor

Zanubrutinib, a covalent BTK inhibitor, has shown efficacy and improved selectivity in early-phase trials on several B-cell hematological malignancies, including CLL. In the US, zanubrutinib is approved for any-line treatment of Waldenström macroglobulinemia, as well as relapsed or refractory mantle cell lymphoma and marginal zone lymphoma. Pivotal trials also showed zanubrutinib had similar or superior efficacy and reduced incidence of atrial fibrillation in patients with Waldenström macroglobulinemia and relapsed or refractory CLL.

The SEQUOIA Trial

The SEQUOIA trial was an open-label, multicenter, randomized, controlled, phase 3 trial to evaluate the potential benefits of zanubrutinib versus bendamustine and rituximab chemoimmunotherapy in patients with treatment-naïve CLL who were older or had comorbidities.

In the report, published in *The Lancet Oncology*, researchers wrote that zanubrutinib significantly improved PFS compared with bendamustine plus rituximab in patients with untreated CLL and SLL and had a safety profile comparable with published data.

The trial was performed in 153 academic or community hospitals across 14 countries or regions and enrolled 590 patients from Oct. 31, 2017, to July 22, 2019. Eligible patients had treatment-naïve CLL or SLL and were aged 65 years or older or 18 years or older with comorbidities, had an Eastern Cooperative Oncology Group performance status score of zero to two, and met at least one indication for treatment per International Workshop on CLL criteria.

Participants were ineligible for fludarabine, cyclophosphamide, and rituximab treatment based on age, a Cumulative Illness Rating Scale score greater than six, creatinine clearance less than 70 mL/min, or a history of frequent or severe infections. The authors noted that bendamustine and rituximab chemoimmunotherapy was considered standard of care for untreated CLL in participating countries and was accepted by regulatory authorities as a comparator for SEQUOIA.

Other patient characteristics included:

- Median age of 70 years (interquartile range [IQR], 66-74 years)
- Unmutated immunoglobulin heavy chain variable (IGHV) in 246 of 465 patients (53%) with evaluable data
- Bulky disease in 142 of 479 patients (30%)
- Binet stage C disease in 140 of 479 patients (29%)

Patients without the high-risk genomic abnormality chromosome 17p13.1 deletion syndrome were randomly assigned to receive zanubrutinib (group A; n=241) or bendamustine plus rituximab (group B; n=238). Patients with chromosome 17p13.1 deletion syndrome were assigned to receive zanubrutinib in a separate group (group C; n=111). Randomization was done using a sequential block method with a random block size of four.

Groups A and B were stratified by age (<65 years vs ≥65 years), Binet stage (C vs A/B), IGHV variable region mutational status (mutated vs unmutated), and geographical region (North America vs Europe vs Asia-Pacific) for subgroup analyses.

Group A received oral zanubrutinib 160 mg twice daily over 28-day cycles. Group B received intravenous bendamustine 90 mg/m² of body surface area on days one and two for six cycles with rituximab 375 mg/m² of body surface area on the day prior or day one of the first cycle and rituximab 500 mg/m² of body surface area on the first day of cycles two through six.

Patients in group B with centrally confirmed disease progression were eligible to cross over to zanubrutinib. Dose modifications were allowed in order to manage adverse events, infection prophylaxis was left to participating institutions' standard practice, and patients could leave the study due to withdrawal, loss of follow-up, or death.

Baseline screening assessments recorded participants' high-risk disease characteristics (including IGHV mutations via DNA sequencing and genetic abnormalities associated with CLL via fluorescence in situ hybridization). Computed tomography imaging of the neck, chest, abdomen, and pelvis with and without contrast was performed at baseline and every 12 weeks for 96 weeks, followed by every 24 weeks until progression.

The primary end point of the trial was PFS in the intention-to-treat patients in groups A and B, as assessed by an independent review committee. Treatment superiority was defined with a two-sided α minimum of 0.05, and the safety analyses included all patients who received at least one dose of treatment. Complete responses required confirmation via bone marrow examination.

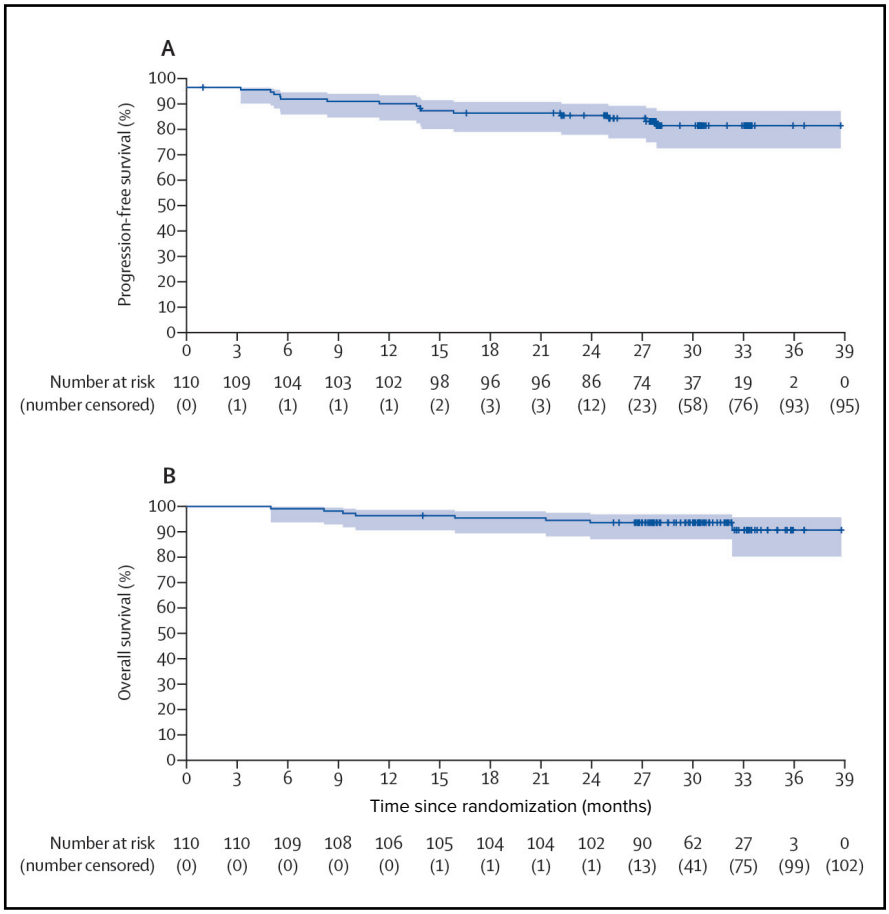

FIGURE. Progression-free survival per independent review committee assessment and overall survival for patients with del(17)(p13·1) **(A)** Kaplan-Meier estimate of progression-free survival among patients in group C. **(B)** Kaplan-Meier estimate of overall survival among patients in group C. All assessments were performed by independent review committee and in the efficacy population. Tick marks denote censored patients.

Findings

The researchers calculated that 450 patients with 118 PFS events provided the study with an 83.5% power to identify a 42% (hazard ratio [HR], 0.58) reduced risk for progression or death for zanubrutinib versus bendamustine.

Over a median follow-up of 26.2 months (IQR, 23.7-29.6 months) at the interim data cutoff of July 27, 2021, 36 (15%) of 241 patients in group A and 71 (30%) of 238 patients in group B had progressed or died per independent review.

The difference in PFS between the groups met prespecified criteria for superiority, with median PFS not reached in group A (95% CI, not estimable [NE]) or group B (95% CI, 28.1-NE; HR, 0.42; 95% CI, 0.28-0.63; P<.0001). The 24-month estimated PFS was 85.5% (95% CI, 80.1-89.6) in group A compared with 69.5% in group B (95% CI, 62.4-75.5).

The authors noted the investigator results were similar, with 29 of 241 patients (12%) in group A and 57 of 238 patients (24%) in group B having progressed or died by the data cutoff (HR,

0.42; 95% CI, 0.27-0.66; *P*=.00011).

The independent review committee found PFS was longer with zanubrutinib compared with bendamustine and rituximab, independent of age, sex, and high-risk disease status (Binet stage C, bulky disease, unmutated IGHV, and chromosome 17p13.1 deletion syndrome). In subgroups with IGHV, SLL, and pathogenic *TP53* mutations, the treatment difference was not statistically significant.

Per independent committee review, the overall response rate was 94.6% in group A (n=228/241; 95% CI, 91.0-97.1) and 85.3% in group B (n=203/238; 95% CI, 80.1-89.6). Furthermore, 16 of 241 patients (7%) in group A and 36 of 238 patients (15%) in group B had complete responses. Median duration of response was not reached for group A (95% CI, NE) and was 30.6 months for group B (95% CI, 25.5-NE).

The median OS was not reached in group A (95% CI, NE) nor group B (95% CI, 30.6-NE). Estimated 24-month OS was 94.3% (95% CI, 90.4-96.7) in group A and 94.6% (95% CI, 90.6-96.9) in group B. The authors found no significant difference in OS between the groups (HR, 1.07; 95% CI, 0.51-2.22; *P*=.87). PFS at 24 months in group C, as estimated by the independent review committee, was 88.9% (95% CI, 81.3-93.6). (See **FIGURE**.)

Safety

In safety analyses, the median safety follow-up was 26.4 months (IQR, 24.2-29.5 months) for group A and 25.9 months (IQR, 23.4-29.6 months) for group B. Overall, 206 of 241 patients (85%) in group A completed treatment with a median relative dose intensity of 98.0% (IQR, 95.2-99.7), and 188 of 238 patients (79%) in group B completed six cycles.

Among groups A and B, the most common grade ≥3 adverse event was neutropenia, which occurred in:

- 27 of 240 patients (11%) in group A
- 116 of 227 patients (51%) in group B
- 17 of 111 patients (15%) in group C

Serious adverse events occurred in:

- 88 of 240 patients (37%) in group A
- 113 of 227 patients (50%) in group B
- 45 of 111 patients (41%) in group C

Any-grade atrial fibrillation occurred in eight of 240 patients (3%) in group A and six of 227 patients (3%) in group B. In addition, one patient in group A had nonsustained ventricular tachycardia and myocardial ischemia, after which zanubrutinib was reinitiated without further arrhythmias. One patient in group B with no known cardiac history experienced ongoing ventricular extrasystoles. Major bleeding events occurred in 12 of 240 patients (5%) in group A, four of 227 patients (2%) in group B, and eight of 111 patients (7%) in group C.

Adverse events leading to mortality occurred in 11 patients (5%) in group A, 12 (5%) in group B, and three (3%) in group C. The most common causes for mortality were COVID-19 (n=4 [2%] in group A), diarrhea (n=2 [1%] in group B), and aspiration pneumonia (n=2 [1%] in group B).

Adverse events leading to treatment discontinuation were reported in 20 of 240 patients (8%) in group A and 31 of 227 patients (14%) in group B. The most common causes were COVID-19 (n=5 [2%] in group A), neutropenia (n=4 [2%] in group B), infusion-related reaction, rash, and thrombocytopenia (n=3 each [1%] in group B).

Study Limitations

The authors acknowledged that treatment route, schedule, and duration were dissimilar between the groups, and neither patients nor physicians were blinded. However, the independent review committee was blinded.

Patients with pathogenic *TP53* mutations were not identified at screening and thus were not assigned to group C, although the authors stated the small size of this population did not substantially affect the primary results. In addition, bendamustine and rituximab chemoimmunotherapy was a widely accepted standard of care for patients with CLL, but the authors acknowledged it might not be the preferred option for treatment-naïve CLL in other countries.

Of note, the COVID-19 pandemic prevented some participating centers from finishing all intended examinations, including bone marrow assessments, which could have skewed identification of complete responses. The authors also considered that the pandemic could have affected the safety analyses of group B, as no patients in the group were still receiving treatment at the onset.

Takeaways

Although the researchers of the SEQUOIA trial wrote that studies with longer follow-up are needed to identify differences in OS between zanubrutinib and chemoimmunotherapy more accurately, they nonetheless reported that zanubrutinib had superior PFS compared with bendamustine plus rituximab in their study's population. Investigators noted that their data showing zanubrutinib was effective in patients with chromosome 17p13.1 deletion syndrome were consistent with previously published data.

Moreover, they suggested treatment with zanubrutinib could potentially reduce the incidence of cardiac arrhythmias, while remaining effective in patients with chromosome 17p13.1 deletion syndrome. Ultimately, the authors supported zanubrutinib as a potential treatment option for older patients or those with comorbidities and untreated CLL or SLL.

The study was funded by BeiGene.

FEATURED PAPER

Tam CS, Brown JR, Kahl BS, 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(8):1031-1043.