# Head-to-Head Comparison of Zanubrutinib Versus Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are different localizations of essentially the same disease. Cancerous lymphocytes in CLL and SLL are predominantly found in blood and bone marrow or in lymph nodes and tissues, respectively. CLL mainly develops in older adults and is the most common subtype of leukemia, representing roughly a quarter of all leukemia cases and 1.3% of all cancers.

In recent years, the evolution of targeted therapies has significantly improved the treatment of CLL. However, many patients with CLL or SLL relapse after or are refractory to first-line treatment and must receive additional lines of therapy.

## Targeted Therapies

The first-generation Bruton's tyrosine kinase (BTK) inhibitor ibrutinib is commonly used in patients with relapsed or refractory CLL, but ibrutinib has been associated with notable toxicity concerns, including increased risks of atrial fibrillation, hypertension, and hemorrhage.

Subsequent treatment options include acalabrutinib, another BTK inhibitor (administered with or without obinutuzumab), as well as venetoclax, a B-cell lymphoma-2 inhibitor. While both therapies improved outcomes versus conventional chemoimmunotherapy with reduced safety signals, the development of new BTK inhibitor therapies is ongoing.

The newest second-generation targeted therapy for patients with CLL or SLL is zanubrutinib, a covalent BTK inhibitor designed to improve targeting specificity compared with previous agents. The dose-finding phase 2 trial assessing zanubrutinib identified a recommended dose of 160 mg twice daily after it achieved complete BTK receptor occupancy in peripheral blood mononuclear cell samples and 100% median lymph node BTK occupancy.

In the phase 3 SEQUOIA trial, zanubrutinib significantly improved progression-free survival (PFS) compared with bendamustine and rituximab-based chemoimmunotherapy regimens in patients with treatment-naïve CLL or SLL.[1]

## The ALPINE Trial

After SEQUOIA, the phase 3 ALPINE trial performed a head-to-head comparison of zanubrutinib and ibrutinib in patients with relapsed or refractory CLL or SLL. The preliminary efficacy analyses in ALPINE suggested zanubrutinib resulted in significantly improved overall response compared with ibrutinib.

Once data had matured, researchers showed that zanubrutinib significantly extended PFS and had a more favorable safety profile compared with ibrutinib. ALPINE data were published in *The New England Journal of Medicine*.

ALPINE was an open-label, phase 3, randomized trial conducted at 113 trial sites across 15 countries in North America, Europe, and the Asia-Pacific region from November 1, 2018, to December 14, 2020. The objective of the trial was to compare efficacy, safety, and side effects between zanubrutinib and ibrutinib in patients with relapsed or refractory CLL or SLL. In addition to the ALPINE investigators, the trial was monitored by an independent data and safety committee comprised of experts in CLL and SLL, clinical trial safety monitoring, and statistics.

The primary end point of ALPINE was overall response based on 2008 International Workshop on CLL criteria every 3 months over 2 years and then every 6 months thereafter. Overall response was defined as complete response, complete response with incomplete bone marrow recovery, modular partial response, or partial response.

The primary end point and key secondary end points, including PFS and incidence of atrial fibrillation or flutter, were additionally assessed by a blinded independent central review for

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regulatory filing with the US Food and Drug Administration (FDA). Further end points included partial response with lymphocytosis or better, duration of response, time to treatment failure, overall survival (OS), and safety.

## Patient Characteristics

ALPINE eligibility criteria included:

- Age 18 years or older
- Confirmed diagnosis of CLL or SLL
- Indicated for treatment per International Workshop on CLL criteria
- Relapsed or refractory to at least 1 previous line of therapy
- Measurable disease on imaging

Notable exclusion criteria included previous BTK inhibitor treatment, history of bleeding disorders, active infections, stroke, or intracranial hemorrhage, as well as recent prior cancer or major surgery.

A total of 652 patients were randomized 1:1 to receive zanubrutinib 160 mg twice daily (n=327) or ibrutinib 420 mg once daily (n=325), continuing until disease progression or unacceptable toxicity. The authors noted a sample size of 600 participants was estimated to give the study over 90% power to detect noninferiority of zanubrutinib in regard to overall response.

The study population had a median age of 67 years (range, 35-90 years) and was 81% White and 14% Asian. Additionally:

- 45% had bulky disease status (tumor ≥5 cm in the greatest dimension)
- 73% had unmutated immunoglobulin heavy-chain variable region (*IGHV*) status
- 23% had chromosome 17p13.1 deletion syndrome, *TP53* mutation, or both
- 80% of zanubrutinib patients and 76% of ibrutinib patients previously received chemoimmunotherapy

| | Zanubrutinib | Ibrutinib |
|---|---|---|
| 18-month PFS | 83.3% (95% CI, 78.7-87.0) | 75.0% (95% CI, 69.8-79.4) |
| 24-month PFS | 78.4% (95% CI, 73.3-82.7) | 65.9% (95% CI, 60.1-71.1) |
| Median PFS | Not reached (95% CI, not estimable [NE]) | 34.2 months (95% CI, 33.3-NE) |

**TABLE 1. PFS Outcomes by Treatment**

In addition, patients had received a median of 1 previous line of therapy (range, 1-12 therapies), with 8% having failed more than 3 prior lines of treatment.

Groups were stratified by age, geographic region, refractory disease, chromosome 17p deletion, and *TP53* mutation status. The cohorts had comparable demographic and clinical characteristics at baseline, although researchers noted that the zanubrutinib group had a higher percentage of female patients than the ibrutinib group (35% vs 29%).

## Zanubrutinib Versus Ibrutinib Analyses

The prespecified interim analysis for overall response included the first 415 patients, while the final analysis concluded approximately 12 months after randomization and included all enrolled patients.

Noninferiority was determined according to a stratified Wald test for each stratification variable with a margin threshold (hazard ratio [HR]) of 1.33, and superiority was determined according to a stratified log-rank test with a threshold of two-sided $P<.05$.

If zanubrutinib was noninferior or superior to ibrutinib for overall response, researchers used a hierarchical testing model to evaluate zanubrutinib versus ibrutinib for PFS in the context of 205 events of disease progression or death.

## Efficacy

The percentage of patients meeting the primary end point of overall response in the investigator analysis was 83.5% in the zanubrutinib group and 74.2% in the ibrutinib group, while the independent review committee calculated rates of 86.2% and 75.7%, respectively.

In both the investigator and independent committee assessments, zanubrutinib was superior to ibrutinib for overall response across all prespecified subgroups, including among patients with 17p deletion syndrome, *TP53* mutation, or both. Both assessments also determined that median duration of response was not reached in the zanubrutinib group and was 33.9 months in the ibrutinib group.

The rates of event-free response at 24 months for the zanubrutinib and ibrutinib groups were 79.5% and 71.3%, respectively, according to the investigators' analysis, and were 77.4% and 67.8%, respectively, according to the independent review committee. Investigator analyses also found 89.9% of patients in the zanubrutinib group had a partial response with lymphocytosis or better compared with 82.5% of the ibrutinib group.

At a median follow-up of 29.6 months, patients in the zanubrutinib group exhibited superior PFS, with 87 occurrences of disease progression or death versus 118 in the ibrutinib group (HR, 0.65; 95% CI, 0.49-0.86; $P=.002$) in the investigator analysis and similar findings in the independent analysis (see **TABLE 1**). Increase in lymph node size was the most common presentation of disease progression in both groups.

The authors noted that the ibrutinib group in ALPINE had PFS consistent with previous studies. For example, patients with relapsed or refractory CLL who received ibrutinib in the pivotal RESONATE trial had a PFS at 18 months of 76%, similar to the 75% PFS rate observed at 18 months in ALPINE.

Zanubrutinib improved PFS compared with ibrutinib in subgroup analyses based on age, previous lines of therapy, disease stage, and *IGHV* mutation status. In high-risk subgroups with 17p deletion syndrome, *TP53* mutation, or both, patients who received zanubrutinib had longer PFS compared with those who received ibrutinib.

Specifically, the proportion of high-risk patients without disease progression or death at 24 months was 72.6% (95% CI, 60.3-81.7) for zanubrutinib versus 54.6% (95% CI, 40.7-66.4) for ibrutinib.

Furthermore, investigators calculated 24 events of disease progression or death in high-risk zanubrutinib patients, with 36 events in high-risk ibrutinib patients (HR, 0.53; 95% CI, 0.31-0.88), and the independent review again supported the trial's analysis, finding 23 and 34 events (HR, 0.52; 95% CI, 0.30-0.88), respectively.

Overall, at 24 months, 79.9% (95% CI, 75.1-83.9) of patients in the zanubrutinib group did not experience treatment failure versus 65.0% (95% CI, 59.5-70.0) in the ibrutinib group.

At the final data cutoff, the zanubrutinib group had 48 deaths reported compared with 60 in the ibrutinib group (HR, 0.76; 95% CI, 0.51-1.11), and median OS was not reached for either group.

## Safety

Researchers stated that 17 (5.2%) of 324 zanubrutinib patients experienced any-grade atrial fibrillation or flutter compared with 43 (13.3%) of 324 ibrutinib patients. Grade 3 atrial fibrillation or flutter was reported in 8 (2.5%) and 13 (4.0%) patients, respectively. Of note, 3 zanubrutinib and 5 ibrutinib patients who experienced arrhythmia events had a medical history of atrial fibrillation or flutter.

The ALPINE authors noted the lower incidence of atrial fibrillation seen with zanubrutinib in this study was consistent with findings from the phase 3 ASPEN trial that compared zanubrutinib and ibrutinib in patients with Waldenström's macroglobulinemia. See **TABLES 2** and **3** for more ALPINE safety outcomes.

| | Zanubrutinib (n=327) | Ibrutinib (n=325) |
|---|---|---|
| Discontinuations due to adverse events | 53 (16.2%) | 74 (22.8%) |
| Discontinuations due to disease progression | 24 (7.3%) | 42 (12.9%) |
| Median duration of treatment | 28.4 months (range, 0.4-41.6) | 24.3 months (range, 0.1-45.1) |

**TABLE 2. Safety Outcomes by Treatment**

| | Zanubrutinib | Ibrutinib |
|---|---|---|
| Diarrhea | 16.0% | 24.1% |
| Hypertension | 21.9% | 19.8% |
| Neutropenia | 22.8% | 18.2% |
| COVID-19 | 23.1% | 17.9% |
| Upper respiratory tract infection | 21.0% | 14.2% |

**TABLE 3. Any-Grade Adverse Events Occurring in at Least 20% of Patients**

At a median follow-up of 29.6 months, patients in the zanubrutinib group exhibited superior progression-free survival.

Grade ≥3 adverse events that occurred in at least 15% of patients in either group included neutropenia at 16.0% and 13.9% and hypertension at 14.8% and 11.1% of zanubrutinib and ibrutinib patients, respectively.

Adverse events that lead to death were reported in 33 zanubrutinib and 36 ibrutinib patients. Among these patients, the most common fatal event was infection (n=44), which the investigators noted was primarily related to COVID-19 events.

Notably, the zanubrutinib group showed a lower incidence of cardiac disorders at 21.3% compared with the ibrutinib group at 29.6%. Moreover, treatment discontinuations due to cardiac disorders were reported in 1 (0.3%) patient in the zanubrutinib group versus 14 (4.3%) in the ibrutinib group. Although 6 patients in the ibrutinib group had deaths attributed to cardiac toxicity, 3 of which occurred within 4 months of ibrutinib initiation, the authors noted that all 6 patients had coexisting cardiac conditions.

Any-grade infections occurred in 71.3% of zanubrutinib patients and 73.1% of ibrutinib patients, grade ≥3 infections occurred in 15.1% and 13.6%, respectively, and colony-stimulating growth factor was used in 15.4% and 15.7%, respectively.

## Conclusions

After a median of 29.6 months of follow-up, the researchers determined that zanubrutinib was superior to ibrutinib in terms of PFS in patients with relapsed or refractory CLL or SLL and across all

major subgroups. Zanubrutinib was also superior in terms of overall responses and partial responses with lymphocytosis or better.

These findings were supported by both investigator and independent review committee assessments, as well as sensitivity analyses that considered the possible effects of disease progression due to treatment discontinuation.

of C-terminal Src kinase and human epidermal growth factor receptor 2. Thus, the safety benefit of zanubrutinib could be explained by its greater BTK targeting selectivity.

Although the authors acknowledged that the open-label design could have affected the investigator assessments, they noted the independent review committee was blinded to treatments

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Researchers theorized that the increased efficacy of zanubrutinib was due to a greater occupancy of disease tissue compared with ibrutinib, as well as better maintenance of exposure coverage over the whole treatment period.

In considering the safety findings, researchers cited theories that ibrutinib can increase atrial fibrillation and cardiac damage through off-target inhibition

and nonetheless reported similar PFS and OS outcomes. Additionally, since OS was not statistically different between the treatments, the authors called for studies with longer follow-up to determine any long-term differences in survival.

Nonetheless, the ALPINE authors summarized that, compared with ibrutinib, zanubrutinib yielded superior PFS and overall response with no new safety signals and fewer treatment discontinuations, cardiac events, and deaths among patients with relapsed or refractory CLL or SLL. The results of the ALPINE and SEQUOIA trials ultimately informed the FDA decision to approve zanubrutinib for the treatment of relapsed or refractory CLL in January.[2]

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### FEATURED PAPER

Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2023;388(4):319-332. doi:10.1056/NEJMoa2211582

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