Long-Term Results of Patients Receiving Zanubrutinib in the Phase 3 ALPINE Study Confirm Sustained Benefit of Zanubrutinib in Patients With Relapsed/Refractory Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma: Up to 6 Years of Follow-Up With the Long-Term Extension

Constantine S. Tam,[1] Andrzej Mital,[2] Robert Weinkove,[3] Wojciech Jurczak,[4] Xin Yan,[5] Nataliya Kuptsova-Clarkson,[6] Tian Tian,[6] Megan Wang,[6] Jamie Hirata[6]

[1]Alfred Health and Monash University, Melbourne, VIC, Australia; [2]The University Clinical Centre, Gdańsk, Poland; [3]Wellington Blood & Cancer Centre, Health New Zealand Capital Coast, Hutt Valley, Wellington, New Zealand; [4]Maria Skłodowska-Curie National Research Institute of Oncology, Kraków, Poland; [5]BeOne Medicines Ltd, Shanghai, China; [6]BeOne Medicines Ltd, San Carlos, CA, USA

CONCLUSIONS

- With up to 6 years of follow-up in patients with R/R CLL/SLL, zanubrutinib continued to demonstrate durable efficacy with a sustained PFS benefit and a consistent safety profile. When adjusted for COVID-19, median PFS was 60.3 months for all patients and 50.2 months for patients with del(17p)
- Most patients from the zanubrutinib arm of ALPINE remain on zanubrutinib in LTE1
- The prevalence of key AESIs remained stable or declined over time
- With the longest reported follow-up to date, patients with del(17p) treated with zanubrutinib demonstrated sustained efficacy comparable with the overall population, along with a similar safety profile

INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are standard of care in relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)[1]
- Zanubrutinib, a next-generation BTK inhibitor, was designed for greater BTK specificity and potency than ibrutinib to reduce off-target toxicities and improve efficacy[1]
- The phase 3, randomized ALPINE study (BGB 3111-305; NCT03734016) compared the efficacy and safety of zanubrutinib versus ibrutinib in patients with R/R CLL/small lymphocytic lymphoma (SLL)[1]
  - Zanubrutinib demonstrated statistically and clinically significant superiority over ibrutinib in progression-free survival (PFS) and overall response rate (ORR), with a favorable safety profile[1]
- The BGB-3111-LTE1 study (LTE1; NCT04170283) is a long-term extension study in which eligible patients can enroll following participation in parent studies of zanubrutinib for the treatment of B-cell malignancies, including patients from comparator treatment arms[2,3]
  - Upon completion of the ALPINE study, eligible patients from both treatment arms who chose to continue participation were enrolled in LTE1 for ongoing zanubrutinib treatment or survival follow-up

Aim

- This analysis aimed to provide updated long-term efficacy and safety in patients initially enrolled in the zanubrutinib arm of ALPINE who continued to LTE1, which includes a total of 6 years of follow-up

METHODS

Study Population and Study Design

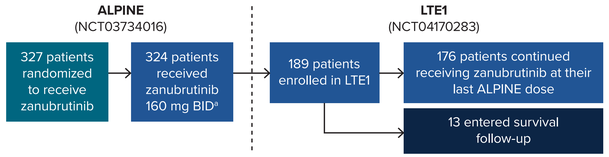
- This ad hoc analysis included all 327 patients in the zanubrutinib arm of ALPINE, with long-term follow-up data for patients who enrolled in LTE1
- In LTE1, patients continued zanubrutinib at their last ALPINE dose
- Efficacy and safety outcomes were evaluated, including PFS per investigator assessment (time from the starting date of zanubrutinib to the date of first documented disease progression or death, whichever is first)
  - Efficacy was assessed at least every 6 months per standard of care with regular restaging scans occurring at investigators' discretion, per the modified 2008 International Workshop on Chronic Lymphocytic Leukemia criteria[4] with modification for treatment-related lymphocytosis for patients with CLL[5] and per the Lugano Classification 2014[6] for non-Hodgkin lymphoma for patients with SLL
  - Safety was assessed every 3 months and included treatment-emergent adverse events (TEAEs) graded per National Cancer Institute Common Terminology Criteria for Adverse Events v5.0

RESULTS

Patient Disposition

- Of the 327 patients enrolled in the zanubrutinib arm of ALPINE, 324 received treatment, and 189 of those patients enrolled in LTE1 between November 9, 2023, and February 28, 2024 (**Figure 1**)

Figure 1. Patient Disposition



[a]Following prespecified toxicities, patients could continue receiving zanubrutinib at a reduced dose (80 mg BID or 80 mg QD). BID, twice daily; QD, once daily.

Patient Characteristics

- Demographics and baseline characteristics of the 327 patients in the zanubrutinib arm of ALPINE were previously reported[1] and are shown in **Table 1**
- 17p deletion [del(17p)] was present in 13.8% of patients

Table 1. Patient Demographics and Baseline Clinical Characteristics

	N=327
Age, years, median (range)	67 (35-90)
Age, years, n (%)	
<65	126 (38.5)
≥65 and <75	127 (38.8)
≥75	74 (22.6)
Gender, n (%)	
Female	114 (34.9)
Male	213 (65.1)
Race, n (%)	
White	261 (79.8)
Black or African American	4 (1.2)
Asian	47 (14.4)
Native Hawaiian or Other Pacific Islander	3 (0.9)
Other[a]	12 (3.7)
ECOG PS, n (%)	
0	129 (39.4)
1	191 (58.4)
2	7 (2.1)
Bulky disease, n (%)	145 (44.3)
Disease stage, n (%)	
Binet stage A or B or Ann Arbor stage I or II	182 (55.7)
Binet stage C or Ann Arbor stage III or IV	145 (44.3)
Del(17p) mutation status, n (%)	
Deleted/abnormal	45 (13.8)
Not deleted/normal	282 (86.2)
Number of prior lines of systemic therapy, median (range)	1 (1-6)

[a]Includes multiple, other, not reported, and unknown. ECOG PS, Eastern Cooperative Oncology Group performance status.

Efficacy Outcomes: PFS

- As of the data cutoff of April 1, 2025, the median follow-up time (ALPINE + LTE1) was 54.2 months (range: 0.1-73.5)
- With a median follow-up (ALPINE + LTE1) of 63.4 months (95% confidence interval [CI]: 57.3-64.5), the median PFS for all patients was 52.5 months (95% CI: 49.7-65.8) and 60.3 months (95% CI: 49.9-not reached [NR]) after COVID-19 adjustment (**Figure 2**)
  - The 60-month PFS rate was 47.3% (95% CI: 41.5-52.9), and when adjusted for deaths due to COVID-19 was 50.4% (95% CI: 44.4-56.1)
- The median follow-up for patients with del(17p) was 56.7 months (95% CI: 55.0-68.0); among these patients, median PFS was 49.9 months (95% CI: 33.3-NR) and 50.2 months (95% CI: 33.3-NR) after COVID-19 adjustment (**Figure 3**)
  - The 60-month PFS rate was 38.2% (95% CI: 23.4-52.9), and when adjusted for deaths due to COVID-19 was 40.5% (95% CI: 25.0-55.5)

Efficacy Outcomes: ORR

- With approximately 12 months of extended follow-up, the complete response (CR)/CR with incomplete bone marrow recovery (CRi) rate continued to increase to 12.8% (95% CI: 9.4-17.0) from 11.6% per the last report,[3] with four patients previously assessed with partial response (PR) having achieved CR/CRi (three with CR and one with CRi) since the ALPINE study closure (**Figure 4**)

Figure 2. PFS in the Overall Population

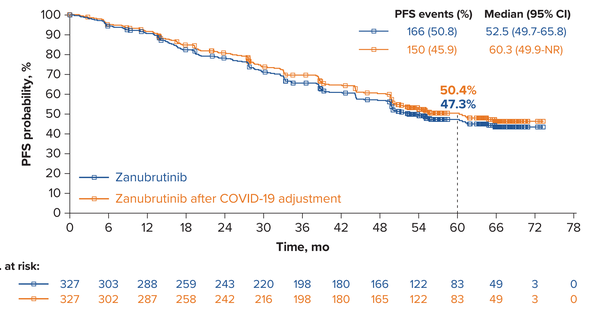


Figure 3. PFS Among Patients with Del(17p)

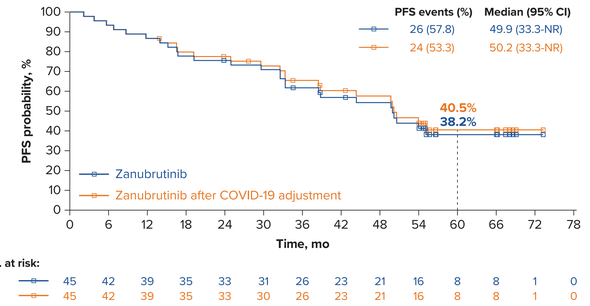
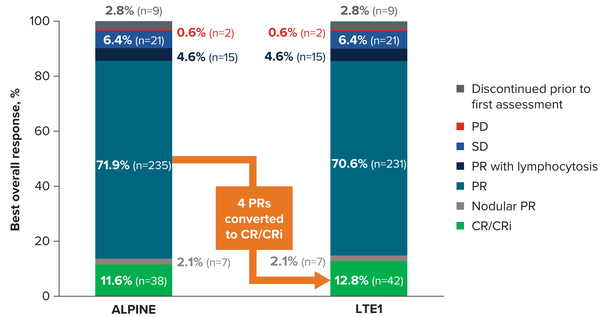


Figure 4. Best Overall Response per Investigator Assessment



PD, progressive disease; SD, stable disease.

Safety

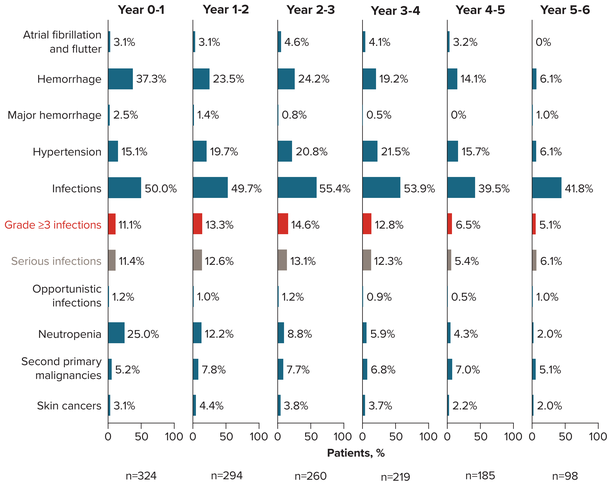
- Among the 324 patients treated with zanubrutinib in ALPINE + LTE1, the median treatment exposure was 52.5 months (range: 0.39-73.4) with 259 patients (79.9%) treated with zanubrutinib for ≥24 months
  - The median exposure among the 45 patients with del(17p) was 40.7 months (range: 0.39-73.4)
- Safety was consistent with previous reports.[1,3] The incidence of TEAEs is summarized in **Table 2**
  - The safety profile in the del(17p) population was comparable with that of the overall safety analysis set (all patients who received ≥1 dose of a study drug)
- The most common any-grade (≥25%)/grade ≥3 (≥10%) TEAEs were COVID-19 (42.3%/10.2%), upper respiratory tract infection (32.7%/2.5%), hypertension (27.5%/16.7%), and neutropenia (25.6%/18.5%), respectively
- COVID-19 pneumonia and COVID-19 were among the most common (≥5%) serious TEAEs, including fatal TEAEs (≥2%), as well as the most common (≥2%) TEAEs leading to treatment discontinuation
- Fatal TEAEs occurred in 14.5% of patients, with the most frequent cause of death being infections (9%), which included COVID-19 pneumonia (2.5%) and COVID-19 (2.2%)

Table 2. Summary of TEAEs

Patients experiencing ≥1 TEAE, n (%)	ALPINE + LTE1 N=324	Del(17p) n=45
Any grade TEAE	323 (99.7)	45 (100.0)
Grade ≥3 TEAE	256 (79.0)	39 (86.7)
Treatment related	137 (42.3)	21 (46.7)
Serious TEAE	195 (60.2)	28 (62.2)
Treatment related	53 (16.4)	10 (22.2)
TEAE leading to treatment discontinuation	66 (20.4)	12 (26.7)
Fatal TEAE	47 (14.5)	8 (17.8)
Treatment related	7 (2.2)	2 (4.4)

- With longer follow-up, the prevalence of most adverse events of special interest (AESIs) remained stable (secondary primary malignancies, atrial fibrillation/flutter, and skin cancer) or declined (hemorrhage including major hemorrhage, hypertension, infections, and neutropenia) over time (**Figure 5**)
  - Both grade ≥3 and serious infections declined over time

Figure 5. Prevalence of Recurrent AESIs Over Time[a]



AESIs are reported as any grade, and colored cerulean, unless otherwise indicated. [a]Time from randomization in ALPINE.

Limitations

- The LTE1 study is a long-term extension of the ALPINE trial and does not contain a comparator arm
- Tumor responses were investigator assessed and not centrally reviewed in the LTE1 study

REFERENCES

1. Brown JR, et al. *N Engl J Med.* 2023;388:319-332.
2. Long-term extension study of zanubrutinib (BGB-3111) regimens in participants with B-cell malignancies. ClinicalTrials.gov identifier: NCT04170283. Updated October 21, 2025. Accessed October 29, 2025. https://clinicaltrials.gov/study/NCT04170283
3. Brown JR, et al. *Blood.* 2024;144:2706-2717.
4. Hallek M, et al. *Blood.* 2008;111:5446-5456.
5. Cheson BD, et al. *J Clin Oncol.* 2012;30:2820-2822.
6. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines Ltd. Medical writing and editorial support was provided by David M. Jensen, PhD of Amiculum, and supported by BeOne Medicines Ltd.

CORRESPONDENCE: Constantine S. Tam, constantine.tam@alfred.org.au

Presented at the 67th American Society of Hematology Annual Meeting and Exposition 2025; December 6–9, 2025; Orlando, FL, USA