# FIRST INTERIM ANALYSIS OF ALPINE STUDY: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB VS IBRUTINIB IN PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

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## Disclosures

**Dr. Hillmen** has received honoraria from Janssen, AbbVie, AstraZeneca, BeiGene, Roche, Pharmacyclics, Sobi, and Alexion; has consulted for Janssen, AbbVie, AstraZeneca, Pharmacyclics, Sobi, and Alexion; received research funding from Janssen, Pharmacyclics, AbbVie, and Apellis, and has participated in a speakers' bureau for Janssen, AstraZeneca, and AbbVie

# Background

- Treatment of CLL/SLL has been transformed with the advent of effective inhibitors of B-cell receptor signaling,[1,2] such as the BTK inhibitor ibrutinib[3,4]
- Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases[5]
- We hypothesized that zanubrutinib may minimize toxicities related to ibrutinib off-target inhibition,[6] and zanubrutinib[5] may improve efficacy outcomes

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

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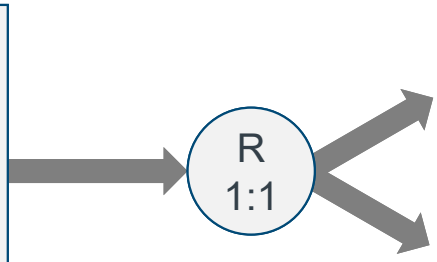
# ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

**R/R CLL/SLL with ≥ 1 prior treatment**
(Planned N=600, Actual N=652)

**Key Inclusion Criteria**
- R/R to ≥1 prior systemic therapy for CLL/SLL
- Measurable lymphadenopathy by CT or MRI

**Key Exclusion Criteria**
- Current or past Richter transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists




**Arm A**
**Zanubrutinib** 160 mg BID

**Arm B**
**Ibrutinib** 420 mg QD

**Stratification Factors**
- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

**Primary Endpoint:** ORR (PR+CR) noninferiority and superiority as assessed by investigator
**Key Secondary Endpoints:** Atrial fibrillation (any grade) and PFS
**Additional Secondary Endpoints:** DOR, OS, time to treatment failure, PR-L or higher, patient-reported outcomes, safety
**Preplanned interim analysis:** Data cutoff approximately 12 months after the randomization of 415 patients;
Data presented here are for the first 415 patients, and efficacy results are per investigator assessment

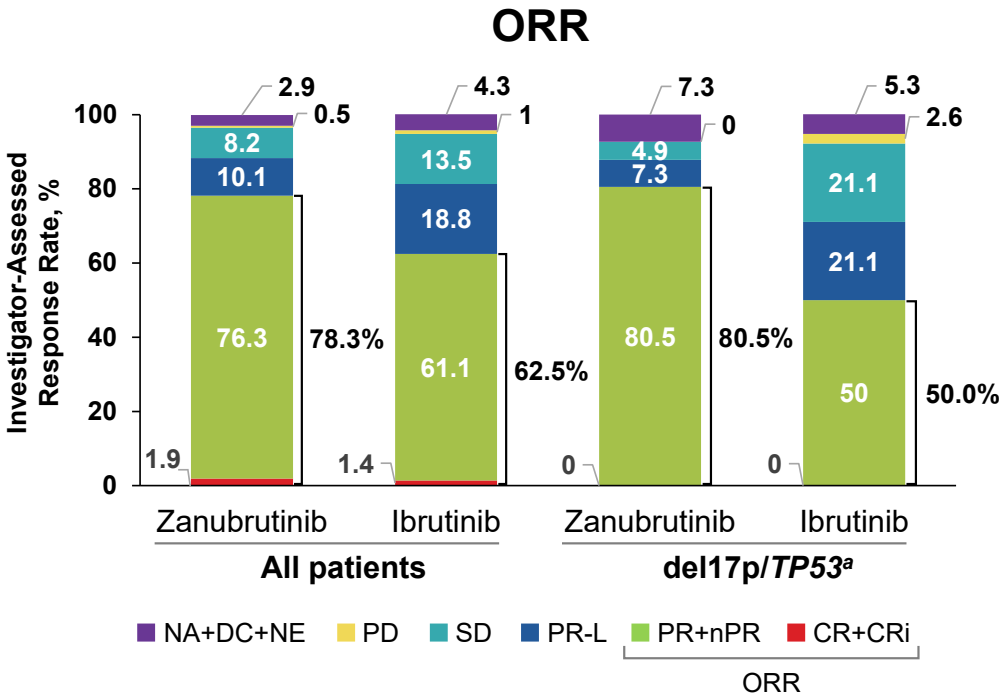
BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CT, computed tomography; DOR, duration of response; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR-L, partial response with lymphocytosis; QD, once daily; R, randomized; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

# Patient Baseline and Disposition

| Characteristic | Zanubrutinib (n=207) | Ibrutinib (n=208) |
|---|---|---|
| Age, median (range)<br>Age ≥65 years, n (%) | 67 (35, 90)<br>129 (62.3) | 67 (36, 89)<br>128 (61.5) |
| Male, n (%) | 142 (68.6) | 156 (75.0) |
| Disease stage, n (%)<br>Binet stage A/B or Ann Arbor stage I/II<br>Binet stage C or Ann Arbor stage III/IV | <br>122 (58.9)<br>85 (41.1) | <br>124 (59.6)<br>84 (40.4) |
| ECOG performance status ≥1, n (%) | 128 (61.8) | 132 (63.5) |
| Prior lines of therapy, median (range)<br>>3 prior lines, n (%) | 1 (1-6)<br>15 (7.3) | 1 (1-8)<br>21 (10.1) |
| Prior chemoimmunotherapy, n (%) | 166 (80.2) | 158 (76.0) |
| del(17p) and/or mutant TP53<br>del(17p), n (%)<br>TP53 mutated, n (%) | 41 (19.8)[a]<br>24 (11.6)<br>29 (14.0)[a] | 38 (18.3)<br>26 (12.5)<br>24 (11.5) |
| del11q, n (%) | 61 (29.5) | 55 (26.4) |
| Bulky disease (≥5 cm), n (%) | 106 (51.2) | 105 (50.5) |
| **Disposition** | **Zanubrutinib (n=207)** | **Ibrutinib (n=208)** |
| Treatment discontinuation<br>Discontinuation due to AEs | 23 (11.1)<br>16 (7.7) | 50 (24.0)<br>27 (13.0) |

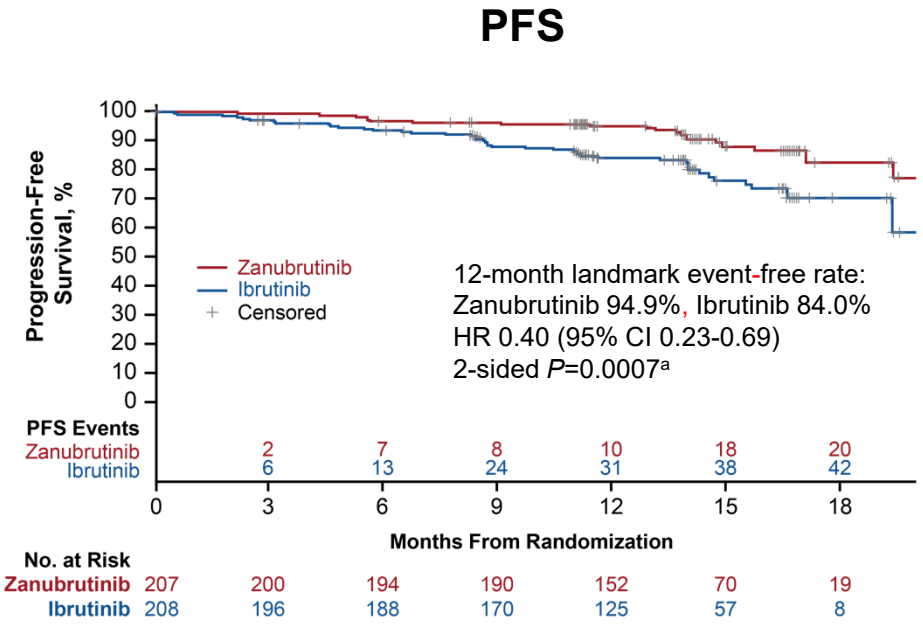
ECOG, Eastern Cooperative Oncology Group.
[a]2 patients with missing values.

# ORR and PFS by Investigator Assessment




[a]In patients with del17p, ORR was zanubrutinib 83.3% and ibrutinib 53.8%.

ORR was significantly[b] higher with zanubrutinib vs ibrutinib

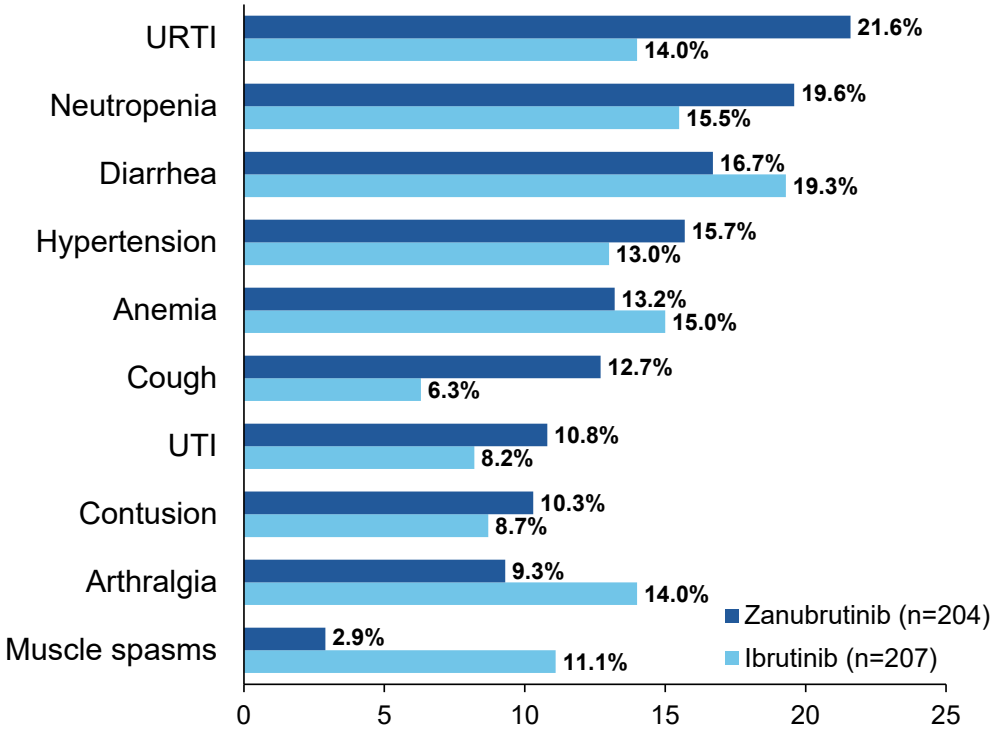



12-month overall survival rates were:
Zanubrutinib 97.0% (11 deaths) and ibrutinib 92.7% (19 deaths)
HR 0.54 (95% CI 0.25-1.16) 2-sided *P*=0.1081[c]

[b]78.3% vs 62.5%, 2-sided *P*=0.0006 compared with prespecified alpha of 0.0099 for interim analysis.
[c]Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.
CR, complete response; CRi, complete response with incomplete bone marrow recovery; DC, discontinuation prior to first assessment; del17p, deletion of the short arm of chromosome 17; HR, hazard ratio; NA, not assessed; NE, not evaluable; nPR, nodular partial response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

# Safety Summary

## Any Grade AEs Occurring in >10% in Either Arm




## AEs of Special Interest

| | Zanubrutinib (n=204), n (%) | | Ibrutinib (n=207), n (%) | |
|---|---|---|---|---|
| **AEs of Special Interest** | **Any Grade** | **Grade ≥3** | **Any Grade** | **Grade ≥3** |
| Cardiac disorders[a] | 28 (13.7) | 5 (2.5) | 52 (25.1) | 14 (6.8) |
| **Atrial fibrillation and flutter[b]** | **5 (2.5)** | **2 (1.0)** | **21 (10.1)** | **4 (1.9)** |
| Hemorrhage<br>Major hemorrhage[c] | 73 (35.8)<br>6 (2.9) | 6 (2.9)<br>6 (2.9) | 75 (36.2)<br>8 (3.9) | 6 (2.9)<br>6 (2.9) |
| Hypertension[d] | 34 (16.7) | 22 (10.8) | 34 (16.4) | 22 (10.6) |
| Infections | 122 (59.8) | 26 (12.7) | 131 (63.3) | 37 (17.9) |
| Neutropenia[e] | 58 (28.4) | 38 (18.6) | 45 (21.7) | 31 (15.0) |
| Thrombocytopenia[e] | 19 (9.3) | 7 (3.4) | 26 (12.6) | 7 (3.4) |
| 2° primary malignancies<br>Skin cancers | 17 (8.3)<br>7 (3.4) | 10 (4.9)<br>3 (1.5) | 13 (6.3)<br>10 (4.8) | 4 (1.9)<br>2 (1.0) |

Safety analysis population.
2°, secondary; AE, adverse events; URTI, Upper respiratory tract infection; UTI, urinary tract infection.
[a]Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients. [b]Key secondary endpoint. [c]Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades. [d]Pooled terms including hypertension and blood pressure increased. [e]Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

## Conclusions

- In this interim analysis of a randomized, phase 3 ALPINE study in patients with relapsed/refractory CLL/SLL, zanubrutinib, compared with ibrutinib, was shown to have:
  - A superior response rate
  - An improved PFS
  - A lower rate of atrial fibrillation/flutter
- These data support that more selective BTK inhibition, with more complete and sustained BTK occupancy, results in improved efficacy and safety outcomes

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# Thank you

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