ZANUBRUTINIB MONOTHERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA: 34-MONTH FOLLOW-UP RESULTS

Abstract 1084090

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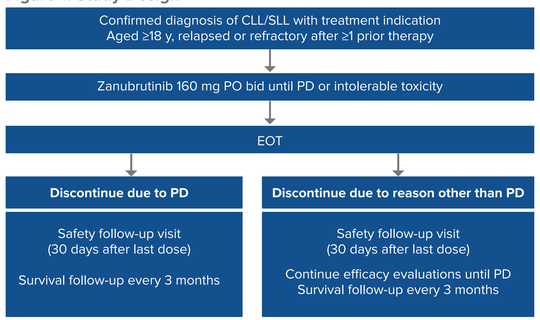
INTRODUCTION

- Zanubrutinib, a highly selective, potent, and irreversible Bruton tyrosine kinase (BTK) inhibitor, was designed to maximize BTK occupancy and minimize off-target inhibition of TEC, ITK, and EGFR-family kinase[1]
- Zanubrutinib has been approved for the treatment of adult patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) in China and for R/R mantle cell lymphoma in both China and the United States
- The previous results of this study reported that zanubrutinib is highly active in R/R CLL/SLL, with a well-tolerated safety profile[2]
- Here, we present the long-term results of a 34-month follow-up of this study

METHODS

- BGB-3111-205 is a single-arm, multicenter, phase 2 study (NCT03206918) of zanubrutinib conducted in China in patients with R/R CLL (**Figure 1**)
- Primary endpoint: Overall response rate (ORR) assessed by independent review committee (IRC) according to International Workshop on CLL guidelines[3] or the Lugano Classification for SLL[4]
- Secondary endpoints: Duration of response and progression-free survival assessed by IRC, and safety

Figure 1. Study Design

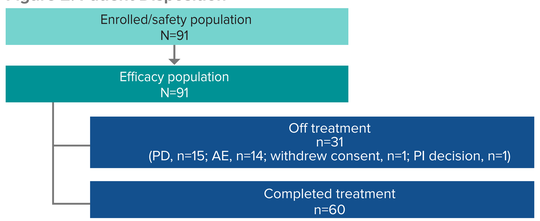


bid, twice daily; CLL, chronic lymphocytic leukemia; EOT, end of treatment; PO, orally; PD, progressive disease; SLL, small lymphocytic lymphoma.

RESULTS

- A total of 91 patients were included in this analysis (**Figure 2**)

Figure 2. Patient Disposition



AE, adverse event; PD, progressive disease; PI, principal investigator

RESULTS (CONTINUED)

- Patient and disease characteristics are described in **Table 1**

Table 1. Patient and Disease Characteristics

Baseline Characteristics	N=91
Median age (range), years	61 (35-87)
Male, n (%)	52 (57.1)
Advanced stage,[a] n (%)	63 (69.2)
Prior therapy, n (%)	
Alkylator (including bendamustine)	68 (74.7)
Purine analog	52 (57.1)
Anti-CD20 antibody	54 (59.3)
Median number of prior lines of therapy (range), n	1 (1-9)
Refractory to last therapy, n (%)	72 (79.1)
ECOG PS 1/2, n (%)	49 (53.8)
Beta-2 microglobulin >3.5 mg/L, n (%)	68 (74.7)
Molecular risk, n (%)	
TP53 mutation and/or 17p deletion	22 (24.2)
IGHV unmutated	51 (56.0)
11q deletion	20 (22.0)
13q deletion	41 (45.1)
Trisomy 12	21 (23.1)

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain; SLL, small lymphocytic lymphoma.
[a]Percentages are based on number of CLL patients with Binet C and SLL patients with stage III and IV.

- Overall response rate was 87.9% (**Table 2**)
- The median follow-up was 34 months (range, 0.8-41.4)

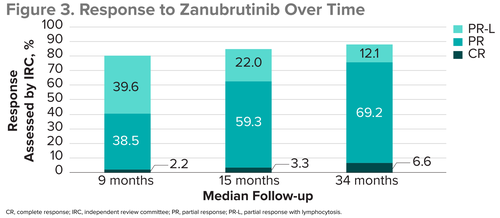
Table 2. Efficacy

Response	N=91
ORR by IRC, n (%) [95% CI]	80 (87.9) [79.4-93.8]
Median TTR, months (range)	2.79 (2.6-16.8)
Best response by IRC, n (%)	
CR	6 (6.6)
PR	63 (69.2)
PR-L	11 (12.1)
SD	3 (3.3)
PD	3 (3.3)
Not evaluable[a]	2 (2.2)
Discontinued prior to first postbaseline assessment	3 (3.3)
Estimated progression/death event-free rate at	
24 months (95% CI) (%)	80.5 (70.5-87.4)
36 months (95% CI) (%)	68.1 (56.6-77.2)
DOR event-free rate at	
24 months (95% CI) (%)	83.4 (73.2-90.0)
36 months (95% CI) (%)	69.9 (57.0-79.6)

CR, complete response; DOR, duration of response; IRC, independent review committee; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; TTR, time to response.
[a]'Not evaluable' was due to missing anatomy imaging of 2 patients.

- Response to zanubrutinib increased and deepened over time (**Figure 3**)

Figure 3. Response to Zanubrutinib Over Time

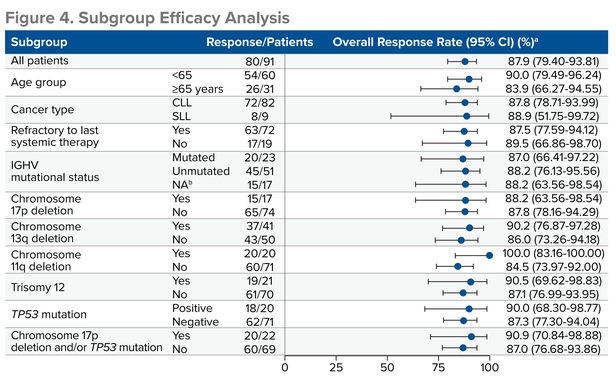


CR, complete response; IRC, independent review committee; PR, partial response; PR-L, partial response with lymphocytosis.

- ORR was generally consistent across all subgroups analyzed, including patients with high-risk cytogenetics (**Figure 4**)
  - Patients with del(17p) and/or *TP53* mutation and del(11q) achieved high response rates of 91% (95% CI, 70.8%-98.9%) and 100% (95%CI, 83.2%-100%), respectively

Figure 4. Subgroup Efficacy Analysis

Subgroup		Response/Patients	Overall Response Rate (95% CI) (%)[a]
All patients		80/91	87.9 (79.40-93.81)
Age group	<65	54/60	90.0 (79.49-96.24)
	≥65 years	26/31	83.9 (66.27-94.55)
Cancer type	CLL	72/82	87.8 (78.71-93.99)
	SLL	8/9	88.9 (51.75-99.72)
Refractory to last systemic therapy	Yes	63/72	87.5 (77.59-94.12)
	No	17/19	89.5 (66.86-98.70)
IGHV mutational status	Mutated	20/23	87.0 (66.41-97.22)
	Unmutated	45/51	88.2 (76.13-95.56)
	NA[b]	15/17	88.2 (63.56-98.54)
Chromosome 17p deletion	Yes	15/17	88.2 (63.56-98.54)
	No	65/74	87.8 (78.16-94.29)
Chromosome 13q deletion	Yes	37/41	90.2 (76.87-97.28)
	No	43/50	86.0 (73.26-94.18)
Chromosome 11q deletion	Yes	20/20	100.0 (83.16-100.00)
	No	60/71	84.5 (73.97-92.00)
Trisomy 12	Yes	19/21	90.5 (69.62-98.83)
	No	61/70	87.1 (76.99-93.95)
TP53 mutation	Positive	18/20	90.0 (68.30-98.77)
	Negative	62/71	87.3 (77.30-94.04)
Chromosome 17p deletion and/or *TP53* mutation	Yes	20/22	90.9 (70.84-98.88)
	No	60/69	87.0 (76.68-93.86)

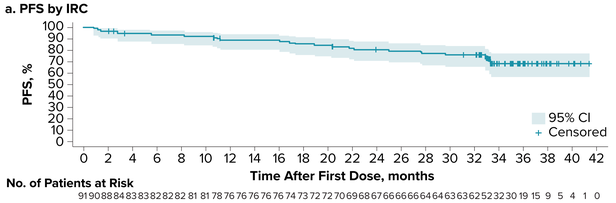


CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain; SLL, small lymphocytic lymphoma.
[a]Two-sided Clopper-Pearson 95% confidence intervals.
[b]NA of IGHV mutational status is for the following cases: IGHV gene rearrangement undetected (3 patients); multiclonal IGHV gene rearrangement detected (13 patients); test failed (1 patient).

- Prolonged lymphocytosis during treatment does not indicate a suboptimal PFS (**Figure 5**)

Figure 5

a. PFS by IRC

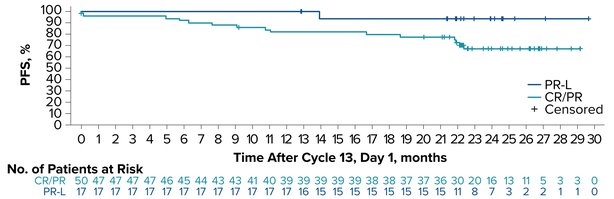


No. of Patients at Risk

91 90 88 84 83 83 82 82 82 81 81 78 76 76 76 76 76 74 73 72 72 70 69 68 67 66 66 66 64 64 63 63 62 52 32 30 19 15 9 5 4 1 0

IRC, independent review committee; PFS, progression-free survival.

b. PFS by Tumor Response



No. of Patients at Risk

CR/PR 50 47 47 47 47 46 45 44 43 43 41 40 39 39 39 39 39 38 38 37 37 36 30 20 16 13 11 5 3 3 0
PR-L 17 17 17 17 17 17 17 17 17 17 17 17 17 16 15 15 15 15 15 15 15 15 11 8 7 3 2 2 1 1 0

CR, complete response; IRC, independent review committee; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis.

- After 34 months of follow-up, safety data are consistent with those previously reported (**Table 3-4, Figure 6**)

Table 3. Safety Summary

Event, n (%)	N=91
Any AE	91 (100)
Grade ≥3 AE	76 (83.5)
Serious AE	47 (51.6)
AEs leading to death[a]	6 (6.6)
AEs leading to treatment discontinuation	14 (15.4)
AE leading to dose interruption	42 (46.2)
AE leading to dose reduction	8 (8.8)

AE, adverse event.
[a]Pneumonia (n=2); 1 each with cardiopulmonary failure, brain herniation, and multiple organ dysfunction syndrome; 1 with cardiac failure, pneumonia, and respiratory failure.

- Most adverse events in regard to lab abnormalities were low severity (grade 1-2) of Common Terminology Criteria for Adverse Events (CTCAE) without clinical consequences
- Only 1 patient reported atrial fibrillation (grade 2)
- Commonly reported treatment emergent adverse events leading to treatment discontinuation included pneumonia (n=4) and hepatitis B (n=2)

Figure 6. Most Common (≥20%) Treatment Emergent Adverse Events

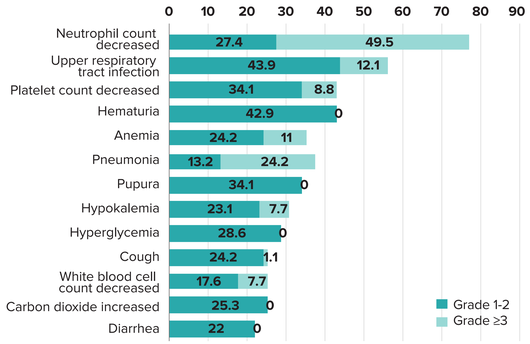


Table 4. Adverse Events of Special Interest[a]

Event, n (%)	All Grade N=91	Grade ≥3 N=91
Anemia	36 (39.6)	10 (11.0)
Hemorrhage	66 (72.5)	1 (1.1)
Major hemorrhage	2 (2.2)	1 (1.1)
Hypertension	11 (12.1)	3 (3.3)
Infections	81 (89.0)	42 (46.2)
Neutropenia	71 (78.0)	46 (50.5)
Second primary malignancies[b]	5 (5.5)	5 (5.5)
Thrombocytopenia	48 (52.7)	15 (16.5)

AESI, adverse events of special interest.
[a]AESIs were summarized based on predefined categories and corresponding search criteria.
[b]Second primary malignancies were reported in 5 patients (2 gastric adenocarcinoma; 1 each of colon cancer, breast cancer, and rectal cancer).

CONCLUSIONS

- Results with longer follow-up continue to show a deeper response in more patients, including those patients with prolonged lymphocytosis at a data cutoff with a median 15-month follow-up
- Deep and durable responses were achieved in all patient subgroups, including patients with high-risk cytogenetics
  - ORRs of 100% were achieved in patients with del(11q) and 91% in patients with del(17p) and/or *TP53* mutation
- Data support the tolerability of long-term zanubrutinib treatment in R/R CLL/SLL, with no new safety signals identified
- Two-thirds of patients were still benefiting from continuous zanubrutinib treatment at the time of data cutoff

REFERENCES

1. Tam CS, et al. *Blood.* 2017;129:2224-2232.
2. Xu W, et al. *J Hematol Oncol.* 2020;13:48.
3. Hallek M, et al. *Blood.* 2008;111:5446-5456.
4. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

DISCLOSURES

WX, SY, KZ, LP, ZL, JZ, SG, DZ, JH, RF, HH, TW and **JL** have nothing to disclose
MJ is an employee of and has equity ownership in BeiGene
HG is an employee of and has equity ownership in BeiGene
JH is an employee of, has a leadership role, equity ownership in, patents, and has received travel expenses from BeiGene
WN is an employee of and has equity ownership in BeiGene
SF is an employee of and has patents with BeiGene and has equity ownership in BeiGene, Amgen, Nektar, Illumina, Annexon, Hutchison China MediTech

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