Conflict of Interest Disclosure – Wei Xu; Oral #49

15–ICML

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Honoraria	None
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Introduction

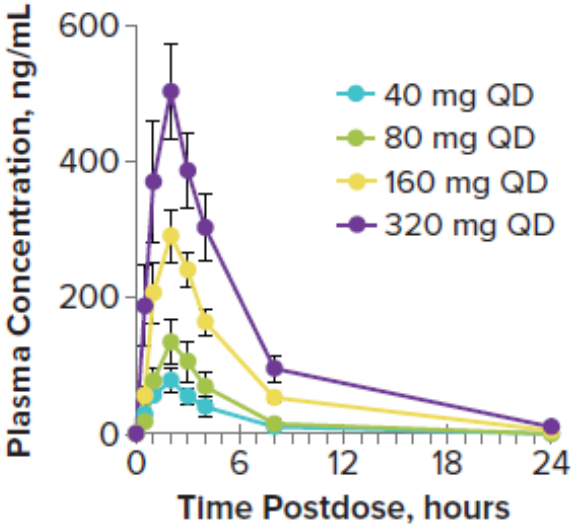
- BTK is a critical component of the B-cell receptor signaling pathway mediating B-cell proliferation, migration, and adhesion.[1-2]
- Zanubrutinib (BGB-3111) is an investigational next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases.[3]
  - Has been shown to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous PK/PD properties.[3]
  - Complete and sustained BTK occupancy observed in both peripheral blood mononuclear cells and in lymph nodes.[3]
- Based on drug interaction studies:
  - Co-administration of proton pump inhibitor (PPIs) or other acid-reducing agents (ARA) does not affect zanubrutinib exposure.
  - Patients have been allowed to receive warfarin and aspirin on zanubrutinib trials.

BTK, Bruton's tyrosine kinase; EGFR, epidermal growth factor receptor; PK/PD, pharmacokinetic/pharmacodynamic.

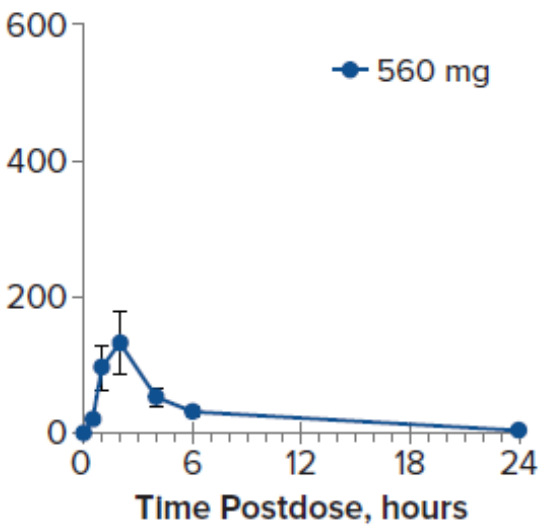
1. Woyach JA, et al. *Blood*. 2012;120(6):1175-1184. 2. Rickert RC. *Nat Rev Immunol*. 2013;13(8):578-591. 3. Tam CS, et al. *Blood*. 2015;126:832.

Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib

Zanubrutinib[1]

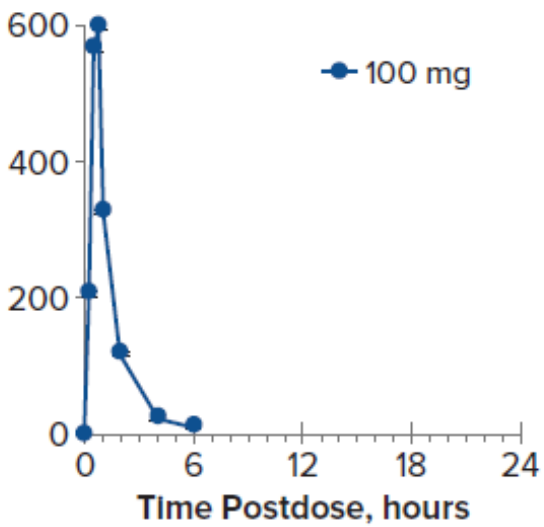


Ibrutinib[2]



Adapted from Advani, et al. *J Clin Oncol*. 2013[2]

Acalabrutinib[3]

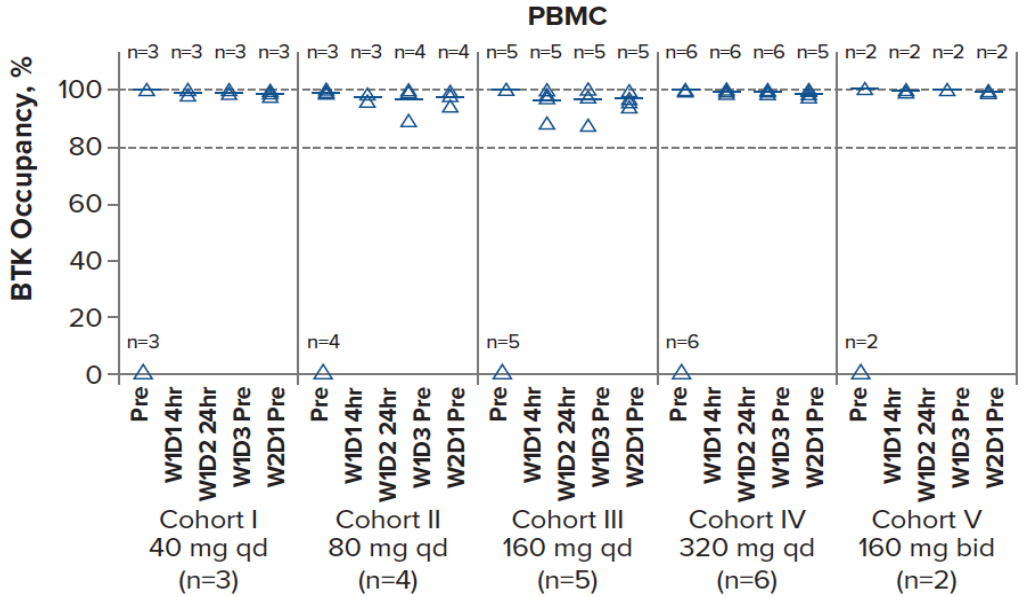


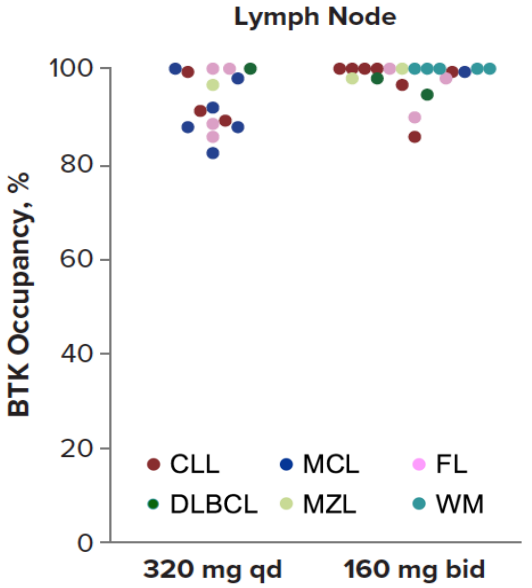
Adapted from Byrd, et al. *New Engl J Med*. 2016[3]

QD, once daily.

1. Tam CS, et al. *Blood*. 2015;126:832 [oral presentation]. 2. Advani RH, et al. *J Clin Oncol*. 2013;31:88-94. 3. Byrd JC, et al. *New Engl J Med*. 2016;374:323-332.

Sustained BTK Inhibition in Peripheral Blood and Lymph Nodes





- Complete and sustained BTK occupancy is seen in paired PBMC (left figure) and lymph node biopsy samples (right figure) collected pre-dose on Day 3. In blood samples, complete BTK occupancy was seen at the lowest dose (40 mg).
- Note, 100% median trough occupancy at a dose of 160 mg twice daily with 94% of subjects having >90% occupancy in lymph nodes across malignancies.

bid, twice daily; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PBMC, peripheral blood mononuclear cells; qd, once daily; WM, Waldenstrom macroglobulinemia.

BGB-3111-205: Multicenter, Open-Label, Single-Arm Trial

- Objectives
  - Primary: IRC-assessed ORR
  - Secondary: PFS, DOR, TTR, safety
  - Exploratory: Biomarkers
- Response assessment:
  - iwCLL 2008 criteria for CLL with 2012 modification for PRL (Hallek, Cheson)[1,2]
  - CT-based assessment according to Lugano Classification for SLL[3]

R/R CLL/SLL Key Criteria

Inclusion Criteria
- ≥18 years old
- At least one treatment indication
- Measurable lesion

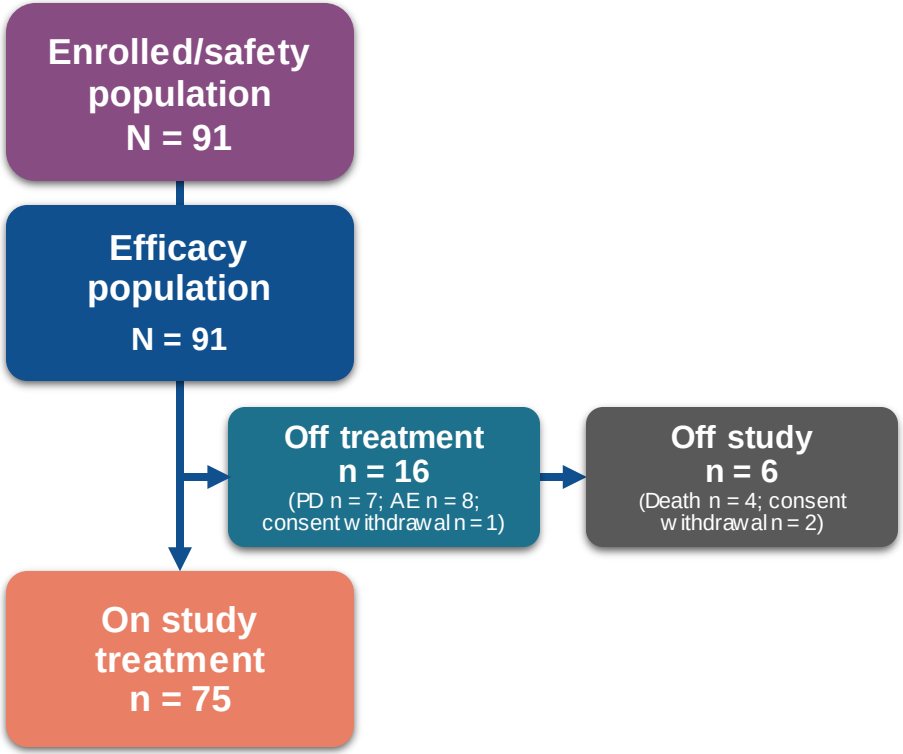
Exclusion Criteria
- Richter syndrome
- Insufficient organ function

Zanubrutinib 160 mg bid until progression, intolerable toxicity, or end of study

bid, twice a day; CLL, chronic lymphocytic leukemia; DOR, duration of response; IRC, independent review committee; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TTR, time to response.

1. Hallek M, et al. *Blood*. 2008;111(12):5446-5456. 2. Cheson BD, et al. *J Clin Oncol*. 2012;30:2820-2822. 3. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3067.

Patient Disposition



- Enrollment was opened from March to December in 2017.
- A total of 91 patients were enrolled from 11 study centers.
  - 82 CLL patients
  - 9 SLL patients
- The median study follow-up time was 15.1 months (range, 0.8 to 21.2).

AE, adverse event; CLL, chronic lymphocytic leukemia; PD, progressive disease; SLL, small lymphocytic lymphoma.

Baseline Characteristics

Baseline Characteristics	N = 91
Median age (range), years	61.0 (35 - 87)
Male, n (%)	52 (57.1)
Late 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)
Refractory to last therapy, n (%)	72 (79.1)
ECOG PS 0/1, n (%)	88 (96.7)
Bulky disease, n (%)	
LDi ≥5 cm	40 (44.4)
Beta-2 microglobulin >3.5 mg/L, n (%)	68 (74.7)

Baseline Characteristics	N = 91
Splenomegaly, n (%)	56 (61.5)
Hepatomegaly, n (%)	11 (12.1)
Absolute lymphocyte count, n (%)	
$<25 \times 10^9$/L	57 (62.6)
$25 – 100 \times 10^9$/L	26 (28.6)
$>100 \times 10^9$/L	8 (8.8)

[a]Percentages are based on number of CLL patients with Binet C and SLL patients with stage III and IV.

CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; LDi, longest diameter; SLL, small lymphocytic leukemia.

Genetic Characteristics

Genetic Characteristics	N = 91
TP53 mutation and/or 17p deletion, n (%)	22 (24.2)
IGHV unmutated, n (%)	51 (56.0)
Cytogenetic abnormalities, n (%)	
17p deletion	17 (18.7)
11q deletion	20 (22.0)
13q deletion	41 (45.1)
Trisomy 12	21 (23.1)

Best Overall Response by IRC

Response by IRC	N = 91
ORR, n (%)	77 (84.6)
BOR, n (%)	
Complete response	3 (3.3)
Partial response	54 (59.3)
Partial response with lymphocytosis	20 (22.0)
Stable disease	4 (4.4)
Progressive disease	4 (4.4)
Not evaluable[a]	3 (3.3)
Discontinued prior to first post-baseline assessment	3 (3.3)

- The ORR was 91.2% (83.4, 96.1) and the PR or higher rate was 72.5% (62.2, 81.4) as assessed by investigators.
- High concordance rate for overall response assessments was 91.2% between IRC and investigator assessments.

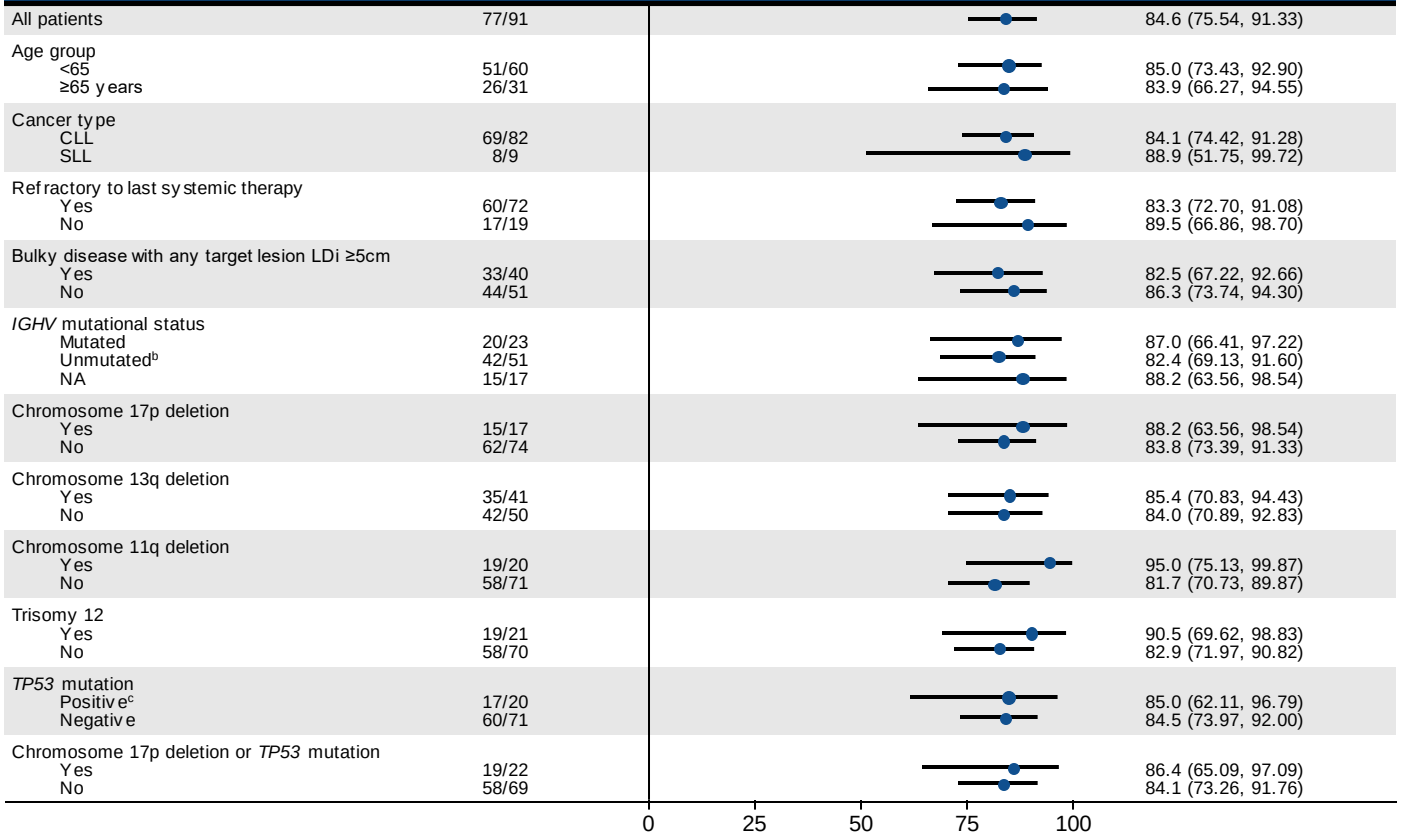
[a]Missing anatomy imaging for 2 patients, and without evidence of response maintenance for at least 2 months for 1 patient, separately.
BOR, best overall response; IRC, independent review committee; ORR, overall response rate; PR, partial response.

Subgroup Efficacy Analysis

Data cut: Dec 14, 2018

- ORRs per IRC were generally consistent across all subgroups.
- The response rates for the 17p deletion or *TP53* mutation subgroup was 86.4%, and 82.4% for the *IGHV* unmutated subgroup.

Subgroup	Response/Subjects	ORR (95% CI) (%)[a]
All patients	77/91	84.6 (75.54, 91.33)
Age group		
<65	51/60	85.0 (73.43, 92.90)
≥65 years	26/31	83.9 (66.27, 94.55)
Cancer type		
CLL	69/82	84.1 (74.42, 91.28)
SLL	8/9	88.9 (51.75, 99.72)
Refractory to last systemic therapy		
Yes	60/72	83.3 (72.70, 91.08)
No	17/19	89.5 (66.86, 98.70)
Bulky disease with any target lesion LDi ≥5cm		
Yes	33/40	82.5 (67.22, 92.66)
No	44/51	86.3 (73.74, 94.30)
IGHV mutational status		
Mutated	20/23	87.0 (66.41, 97.22)
Unmutated[b]	42/51	82.4 (69.13, 91.60)
NA	15/17	88.2 (63.56, 98.54)
Chromosome 17p deletion		
Yes	15/17	88.2 (63.56, 98.54)
No	62/74	83.8 (73.39, 91.33)
Chromosome 13q deletion		
Yes	35/41	85.4 (70.83, 94.43)
No	42/50	84.0 (70.89, 92.83)
Chromosome 11q deletion		
Yes	19/20	95.0 (75.13, 99.87)
No	58/71	81.7 (70.73, 89.87)
Trisomy 12		
Yes	19/21	90.5 (69.62, 98.83)
No	58/70	82.9 (71.97, 90.82)
TP53 mutation		
Positive[c]	17/20	85.0 (62.11, 96.79)
Negative	60/71	84.5 (73.97, 92.00)
Chromosome 17p deletion or *TP53* mutation		
Yes	19/22	86.4 (65.09, 97.09)
No	58/69	84.1 (73.26, 91.76)

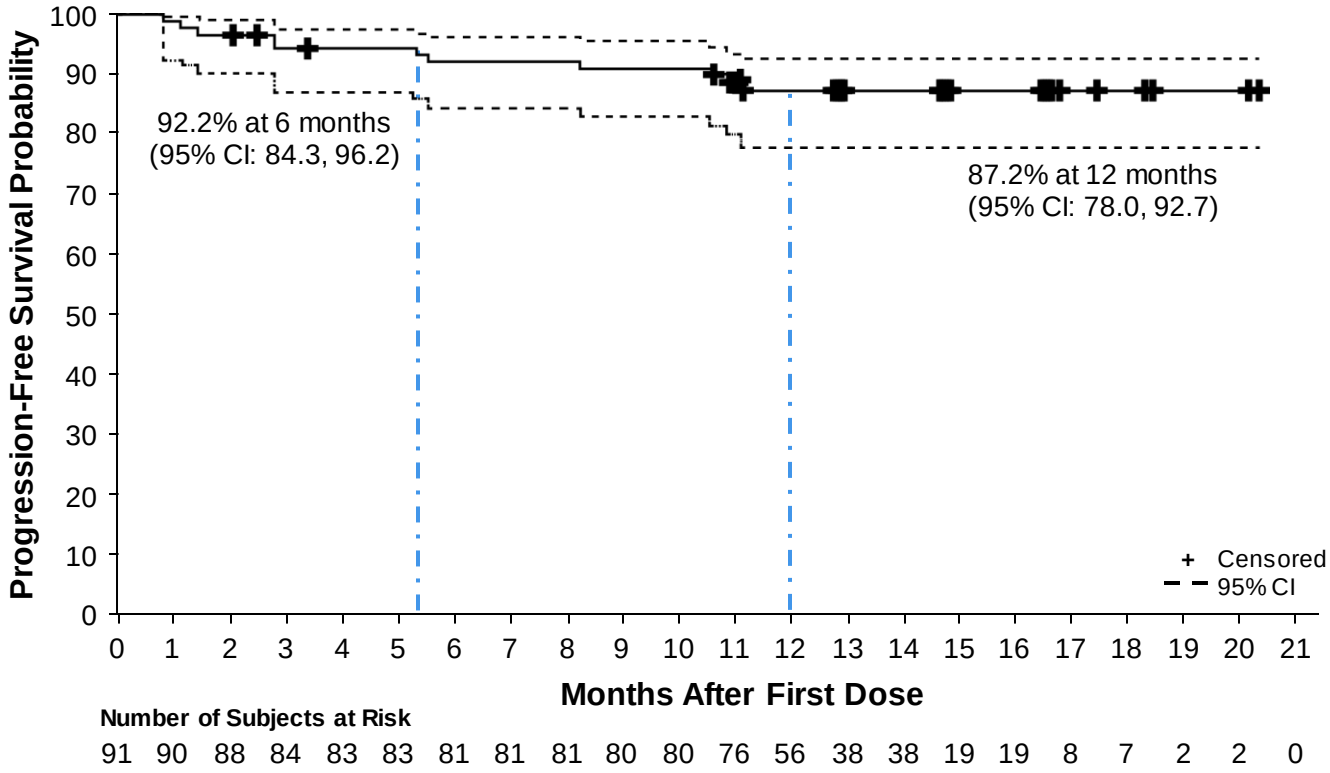


[a]2-side Clopper-Pearson 95% confidence intervals. [b]'NA' of *IGHV* mutational status is for the following cases: *IGHV* gene rearrangement undetected (3 patients); multiclonal *IGHV* gene rearrangement detected (13 patients); test failed (1 patient). [c]Sample from 1 patient was detected as negative with Sanger Sequencing method instead of Next Generation Sequencing.

CI, confidence interval; CLL, chronic lymphocytic leukemia; IRC, independent review committee; LDi, longest diameter; ORR, overall response rate; SLL, small lymphocytic leukemia.

IRC-Assessed PFS

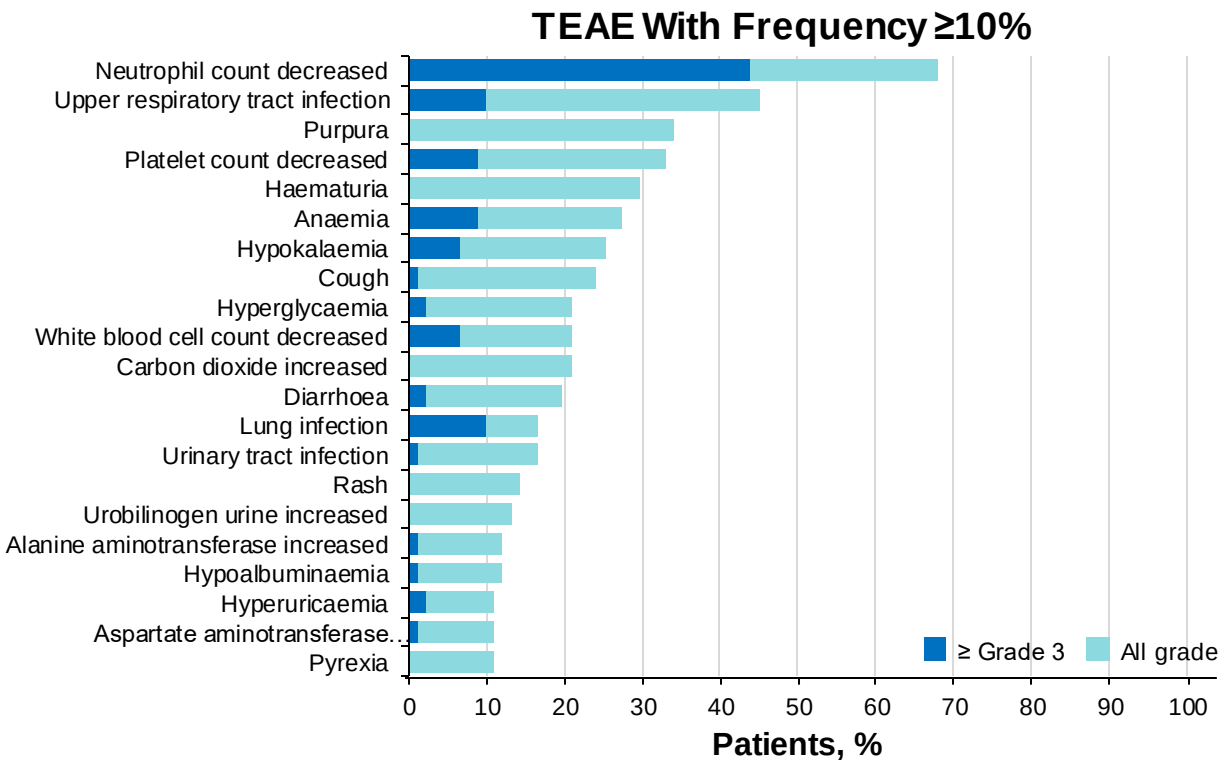
- The median follow-up time for PFS is 12.9 months (0.8, 20.4).
- Median PFS has not been reached.



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

TEAE Regardless of Causality

- Serious AEs were reported in 33% of patients.
- There were 8 patient-reported AEs leading to treatment discontinuation.
- There were 3 patient-reported AEs leading to death, all within 30 days of last dose.
  - Lung infection/cardiac failure/respiratory (unlikely related)
  - Cardiopulmonary failure (unlikely related)
  - MODS (not related) in the setting of disease progression



AE, adverse event; MODS, multiple organ dysfunction syndrome; TEAE, treatment-emergent AE.

Summary

- Zanubrutinib demonstrated a high ORR of 84.6% as assessed by IRC in R/R CLL/SLL patients, including poor prognostic subgroups
  - 86.4% in patients with *TP53* mutation or 17p deletion
  - 82.4% in patients with *IGHV* unmutated
- The safety and tolerability profile shown in Chinese patients with R/R CLL/SLL was consistent with previous reports in CLL/SLL patients.
- Data from study BGB-3111-205 has been submitted to the NMPA seeking approval for zanubrutinib in R/R CLL/SLL.
- Confirmatory studies including a head-to-head study with ibrutinib in R/R patients (BGB-3111-305) and comparison with BR in treatment-naïve patients (BGB-3111-304) are ongoing.

BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; IRC, independent review committee; NMPA, National Medical Products Administration; ORR, overall response rate; R/R, relapsed/refractory; SLL, small lymphocytic leukemia.

Acknowledgments

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Thank You!