Deep and Sustained Responses in Patients With CLL Treated With Zanubrutinib or Zanubrutinib + Obinutuzumab in Phase 1/2 AU-003 and Phase 1b GA-101 Studies: A Report From the Zanubrutinib Extension Study

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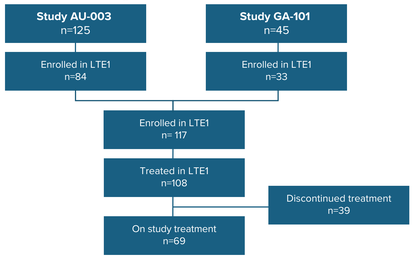
INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors have become a standard of care for patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)[1]
- Zanubrutinib, a next-generation BTK inhibitor, was developed to ensure greater BTK specificity and potency than ibrutinib to avoid toxicities associated with off-target binding and improve efficacy[2]; deep and durable responses with zanubrutinib have been demonstrated in patients with CLL/SLL[3]
- The phase 1/2 AU-003 study (BGB-3111-AU-003; NCT02343120) evaluated zanubrutinib monotherapy in patients with various B-cell malignancies, including CLL/SLL[4]
- The phase 1b GA-101 study (NCT02569476) evaluated zanubrutinib in combination with obinutuzumab (ZO) for 6 cycles followed by continuous zanubrutinib monotherapy in patients with CLL/SLL or follicular lymphoma[5]
- At the end of AU-003 and GA-101, eligible patients could enroll in a long-term extension study, BGB-3111-LTE1 (LTE1, NCT04170283), for continued treatment with zanubrutinib or survival follow-up
- The study design, methods, and results of AU-003 and GA-101 have previously been described[4-6]
- Here, we report safety and efficacy outcomes in patients with CLL/SLL from AU-003 and GA-101, with extended follow-up from the LTE1 study

METHODS

- This ad hoc analysis included all patients with CLL/SLL from AU-003 and GA-101 and incorporated long-term follow-up data from patients who enrolled in LTE1 upon completion of these studies
- In the LTE1 study, safety outcomes, including the occurrence of treatment-emergent adverse events (TEAEs), were evaluated at least every 3 months
- Investigators assessed disease response at least every 6 months in LTE1, using modified International Workshop on Chronic Lymphocytic Leukemia (iWCLL) guidelines[7,8]; investigators could also assess "no evidence of progressive disease"
- PFS and OS estimates were calculated using the Kaplan-Meier method both with and without adjustments for the potential impact of the COVID-19 pandemic, with censoring of deaths due to COVID-19

Figure 1. CONSORT Diagram



RESULTS

Disposition

- Between January 18, 2020, and March 17, 2021, 117 patients treated with zanubrutinib monotherapy in AU-003, or ZO in GA-101, enrolled in LTE1 (**Figure 1**)
  - Patient and disease characteristics are shown in **Table 1**
  - At enrollment in LTE1, the median time since zanubrutinib treatment initiation was 44.1 months overall (range, 20.0-71.6 months), and was 47.9 months (range, 38.6-65.3) and 40.5 months (range, 20.0-71.6 months) in patients with treatment-naive (TN) and relapsed/refractory (R/R) CLL/SLL, respectively
- As of April 15, 2024, 69 patients (40.6%) remained on study treatment; the median follow-up time (parent study + LTE1) was 78.1 months (range, 5.3-106.9 months), and the median zanubrutinib treatment duration was 67.9 months (range, 0.8-106.9 months)

Table 1. Baseline Demographics and Clinical Characteristics

	At Initial Study Enrollment: AU-003 or GA-101			At LTE1 Enrollment after AU-003 or GA-101 End of Study		
	AU-003 (n=125)	GA-101 (n=45)	Overall (N=170)	AU-003 (n=84)	GA-101 (n=33)	Overall (N=117)
Age, median (range), years	67 (24-87)	68 (38-82)	68 (24-87)	72 (40-91)	71 (42-85)	71 (40-91)
Age group, n (%)						
<65 years	51 (40.8)	14 (31.1)	65 (38.2)	22 (26.2)	7 (21.2)	29 (24.8)
≥65 and <75 years	53 (42.4)	20 (44.4)	73 (42.9)	33 (39.3)	16 (48.5)	49 (41.9)
≥75 years	21 (16.8)	11 (24.4)	32 (18.8)	29 (34.5)	10 (30.3)	39 (33.3)
Male, n (%)	93 (74.4)	32 (71.1)	125 (73.5)			
Treatment status, n (%)						
TN	22 (17.6)	20 (44.4)	42 (24.7)			
R/R	103 (82.4)	25 (55.6)	128 (75.3)			
No. of prior lines						
Median (range)	2 (1-10)	1 (1-4)	1 (1-10)			
Mean (SD)	2.1 (1.51)	1.6 (0.91)	2.0 (1.43)			
Mutation status, n/N (%)						
Del(17p) positive[a]	16 (12.8)	13 (28.9)	29 (17.1)			
TP53 positive[b]	14 (11.2)	17 (37.8)	31 (18.2)			
ECOG performance status, n (%)						
0				54 (64.3)	18 (54.5)	72 (61.5)
1				20 (23.8)	9 (27.3)	29 (24.8)
2				1 (1.2)	2 (6.1)	3 (2.6)
3				1 (1.2)	0	1 (0.9)
Missing				8 (9.5)	4 (12.1)	12 (10.3)

[a] *Del(17p)* was present in 19.0% of TN patients and 16.4% of patients with R/R disease. Mutation analysis data was missing for 24 patients in AU-003 and 32 patients in GA-101. [b] *TP53* mutation was present in 21.4% of TN patients and 17.2% of patients with R/R disease. Mutation analysis data was missing for 81 patients in AU-003 and 9 patients in GA-101.
ECOG, Eastern Cooperative Oncology Group; R/R, relapsed/refractory; TN, treatment naive.

Safety Results

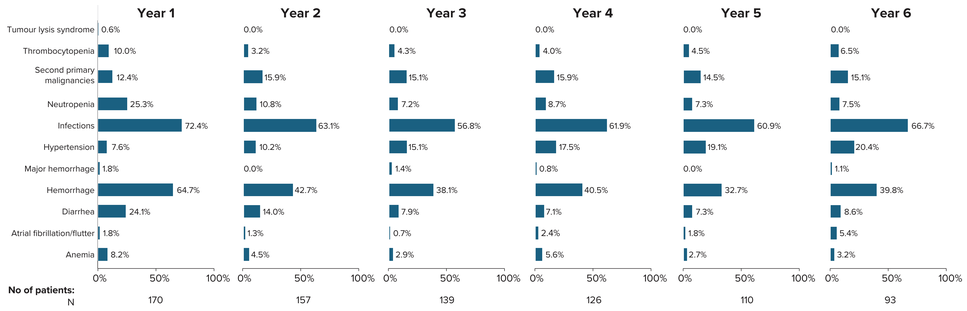
- Grade ≥3 and serious TEAEs occurred in 84.1% and 69.4% of patients, respectively, as presented in **Table 2**
  - 12 deaths occurred in AU-003/GA-101 through LTE1; 2 were due to COVID-19
- The prevalence of cytopenias (neutropenia, anemia, and thrombocytopenia), diarrhea, and hemorrhage decreased over time (**Figure 2**)

Table 2. Summary of TEAEs in AU-003/GA-101 through LTE1

Patients With ≥1 TEAE, n (%)	AU-003 (n=125)	GA-101 (n=45)	Overall (N=170)
TEAE	125 (100.0)	45 (100.0)	170 (100.0)
Treatment related	110 (88.0)	42 (93.3)	152 (89.4)
Serious	90 (72.0)	28 (62.2)	118 (69.4)
Treatment related	40 (32.0)	11 (24.4)	51 (30.0)
Grade ≥3	104 (83.2)	39 (86.7)	143 (84.1)
Treatment related	58 (46.4)	26 (57.8)	84 (49.4)
Leading to treatment discontinuation	17 (13.6)[a]	6 (13.3)[b]	23 (13.5)
Leading to dose reduction	19 (15.2)	3 (6.7)	22 (12.9)
Fatal TEAE	6 (4.8)[c]	6 (13.3)[d]	12 (7.1)

[a] Pneumonia (n=3), anemia, chronic myeloid leukemia, COVID-19, dysphagia, encephalopathy, multiple organ dysfunction syndrome, muscular weakness, periorbital edema, pleural effusion, pneumonia cryptococcal, tachycardia, recurrent skin squamous cell carcinoma, superficial inflammatory dermatosis, urinary tract infection (n=1 for each). [b] Erythema nodosum, disseminated cryptococcus, metastatic prostate cancer, metastatic skin squamous cell carcinoma, pneumonia, sepsis (n=1 for each). [c] COVID-19, oropharyngeal squamous cell carcinoma, pneumonia, respiratory failure, recurrent skin squamous cell carcinoma, subdural hematoma (n=1 for each). [d] Cardiac arrest, COVID-19 pneumonia, general health deterioration, myocardial infarction, sepsis, metastatic skin squamous cell carcinoma (n=1 for each)
TEAE, treatment-emergent adverse event.

Figure 2. Prevalence of Recurrent TEAEs of Special Interest Over Time



Efficacy Results

- In patients receiving zanubrutinib monotherapy (AU-003), with a median follow-up of 76 months (range, 5.3-106.9 months), the overall response rate (ORR; partial response with lymphocytosis or better) was 100% (95% CI, 84.6%-100%) in TN patients and 94.2% (95% CI, 87.8%-97.8%) in patients with R/R CLL/SLL; the complete response (CR)/CR with incomplete count recovery (CRi) rate was 36.4% (95% CI, 17.2%-59.3%) in TN patients and 25.2% (95% CI, 17.2%-34.8%) in patients with R/R CLL/SLL (**Table 3**)
- In patients receiving ZO (GA-101), with a median follow-up of 88.1 months (range, 7.9-98.5 months), the ORR was 100% (95% CI, 83.2%-100%) in TN patients and 92.0% (95% CI, 74.0%-99.0%) in patients with R/R CLL/SLL; the CR/CRi rate was 60.0% (95% CI, 36.1%-80.9%) in TN patients and 36.0% (95% CI, 18.0%-57.5%) in patients with R/R CLL/SLL (**Table 3**)
- The COVID-19–adjusted progression-free survival, overall survival, and duration of response are shown in **Table 4**, **Figure 3**, and **Figure 4**

Table 3. Best Overall Response in AU-003/GA-101 through LTE1

	AU-003		GA-101	
n (%)	TN (n=22)	R/R (n=103)	TN (n=20)	R/R (n=25)
ORR (PR-L or better)	22 (100.0)	97 (94.2)	20 (100.0)	23 (92.0)
CR/CRi	8 (36.4)	26 (25.2)	12 (60.0)	9 (36.0)
95% CI	17.2-59.3	17.2-34.8	36.1-80.9	18.0-57.5
PR	14 (63.6)	68 (66.0)	7 (35.0)	14 (56.0)
PR or better	22 (100.0)	95 (92.2)	20 (100.0)	23 (92.0)
95% CI	84.6-100.0	85.3-96.6	83.2-100.0	74.0-99.0
SD	0	4 (3.9)	0	2 (8)
PD	0	0	0	0
Discontinued prior to assessment	0	1 (1)	0	0

BOR, best overall response; CR, complete response; CRi, complete response with incomplete bone marrow recovery; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

CONCLUSIONS

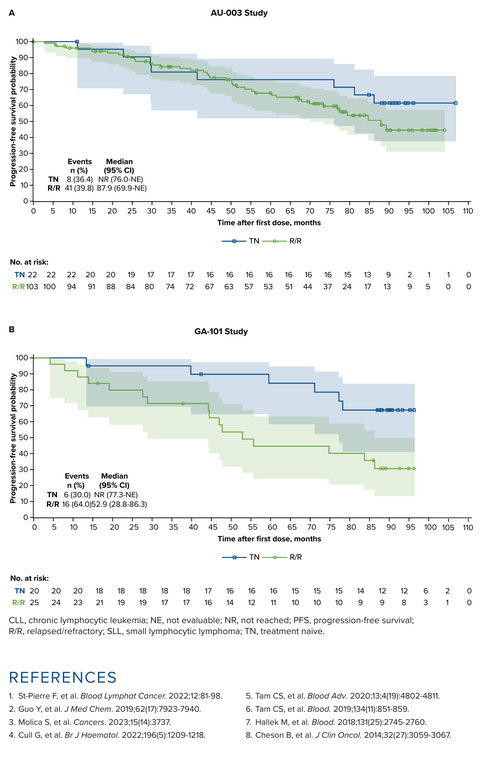
- In patients with CLL/SLL, treatment with zanubrutinib in AU-003 and with ZO in GA-101 led to high rates of overall and complete response, with unprecedented CR/CRi rates for BTKi treatment in TN patients
- With the longest follow-up to date (median 6.5 years), treatment with zanubrutinib or ZO resulted in durable responses and impressive PFS in patients with both TN and R/R CLL/SLL
- The tolerability/safety profile of zanubrutinib, alone and in combination with obinutuzumab, remained favorable, with decreasing prevalence of most TEAEs of interest from the initial treatment period

Table 4. COVID-Adjusted PFS, OS, and DOR in AU-003/GA-101 through LTE1

	AU-003		GA-101	
	TN (n=22)	R/R (n=103)	TN (n=20)	R/R (n=25)
COVID-19–adjusted median PFS (95% CI), mo	89.2 (77.4-NE)		83.7 (55.7-NE)	
72-month event-free rate (95% CI), %	76.2 (51.9-89.3)	61.1 (49.8-70.5)	78.5 (52.3-91.4)	44.6 (24.3-63.2)
COVID-19–adjusted median OS (95% CI), mo	NR		NR	
72-month event-free rate (95% CI), %	90.5 (67.0-97.5)	81.5 (71.8-88.1)	89.5 (64.1-97.3)	63.0 (40.8-78.8)
DOR (95% CI), mo	86.6 (76.6-NE)		83.5 (53.1-NE)	

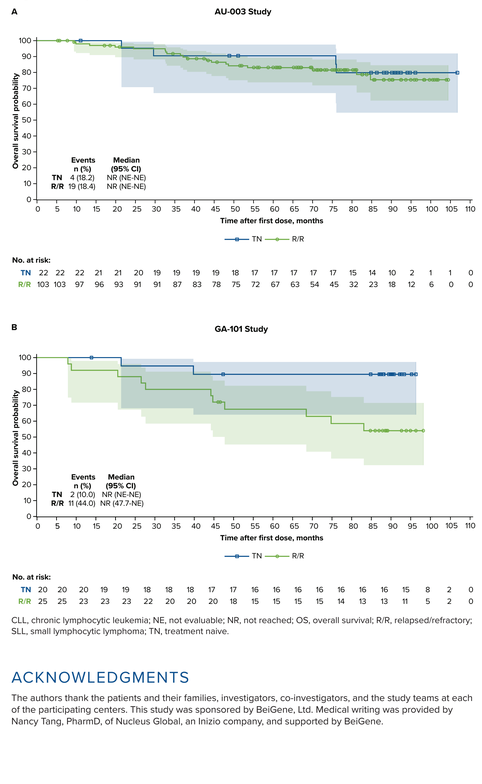
DOR, duration of response; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment naive.

Figure 3. Kaplan-Meier Plot for COVID-Adjusted PFS



CLL, chronic lymphocytic leukemia; NE, not evaluable; NR, not reached; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment naive.

Figure 4. Kaplan-Meier Plot for COVID-Adjusted OS



CLL, chronic lymphocytic leukemia; NE, not evaluable; NR, not reached; OS, overall survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment naive.

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