

# 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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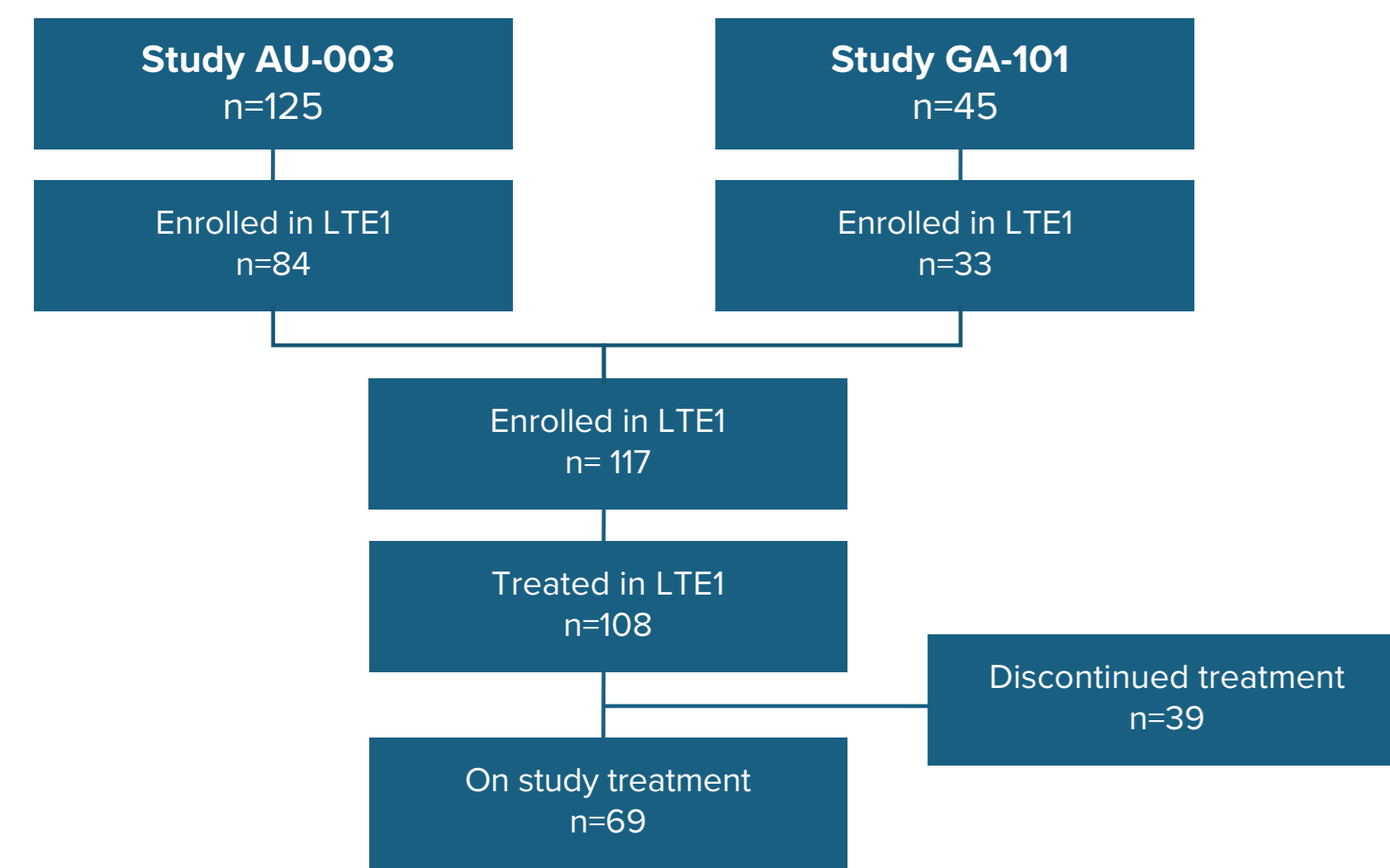
## INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors have become a standard of care for patients with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)<sup>1</sup>
- 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<sup>2</sup>; deep and durable responses with zanubrutinib have been demonstrated in patients with CLL/SLL<sup>3</sup>
- 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<sup>4</sup>
- 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<sup>5</sup>
- 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<sup>4,6</sup>
- 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<sup>7,8</sup>; 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-naïve (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)
<b>Age, median (range), years</b>	67 (24-87)	68 (38-82)	68 (24-87)	72 (40-91)	71 (42-85)	71 (40-91)
<b>Age group, n (%)</b>						
<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)
<b>Male, n (%)</b>	93 (74.4)	32 (71.1)	125 (73.5)			
<b>Treatment status, n (%)</b>						
TN	22 (17.6)	20 (44.4)	42 (24.7)			
R/R	103 (82.4)	25 (55.6)	128 (75.3)			
<b>No. of prior lines</b>						
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)			
<b>Mutation status, n/N (%)</b>						
<i>De(17p)</i> positive <sup>a</sup>	16 (12.8)	13 (28.9)	29 (17.1)			
<i>TP53</i> positive <sup>b</sup>	14 (11.2)	17 (37.8)	31 (18.2)			

<sup>a</sup>*De(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. <sup>b</sup>*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 naïve.

### Safety Results

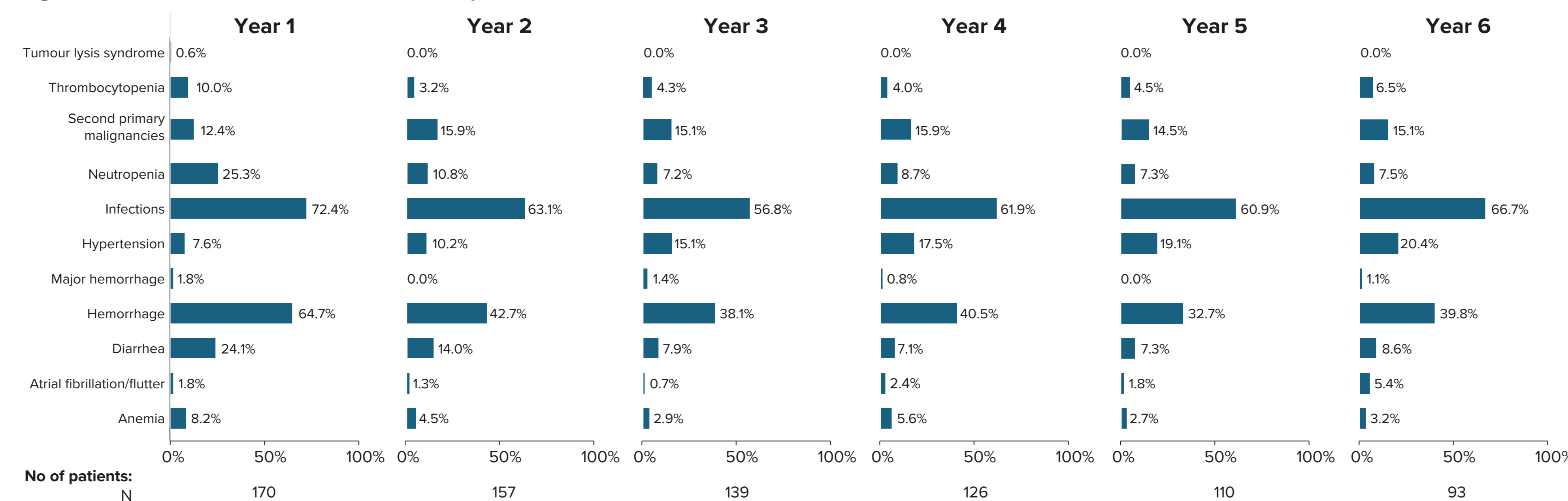
- Grade ≥3 and serious TEAEs occurred in 84.1% and 69.4% of patients, respectively, as presented in Table 2
- 12 deaths occurred in AU-003/GA-101 through LTE1; 2 were due to COVID-19
- The prevalence of cytopenias (neutropenia, anemia, and thrombocytopenia), diarrhea, and hemorrhage decreased over time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

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

	AU-003 (n=125)	GA-101 (n=45)	Overall (N=170)
<b>Patients With ≥1 TEAE, n (%)</b>	125 (100.0)	45 (100.0)	170 (100.0)
<b>TEAE</b>			
Treatment related	110 (88.0)	42 (93.3)	152 (89.4)
<b>Serious</b>			
Treatment related	40 (32.0)	11 (24.4)	51 (30.0)
<b>Grade ≥3</b>			
Treatment related	58 (46.4)	26 (57.8)	84 (49.4)
<b>Leading to treatment discontinuation</b>	17 (13.6) <sup>a</sup>	6 (13.3) <sup>b</sup>	23 (13.5)
<b>Leading to dose reduction</b>	19 (15.2)	3 (6.7)	22 (12.9)
<b>Fatal TEAE</b>	6 (4.8) <sup>c</sup>	6 (13.3) <sup>d</sup>	12 (7.1)

<sup>a</sup>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 dermatitis, urinary tract infection (n=1 for each). <sup>b</sup>Erythema nodosum, disseminated cryptococcus, metastatic prostate cancer, metastatic skin squamous cell carcinoma, pneumonia, sepsis (n=1 for each). <sup>c</sup>COVID-19, oropharyngeal squamous cell carcinoma, pneumonia, respiratory failure, recurrent skin squamous cell carcinoma, subdural hematoma (n=1 for each). <sup>d</sup>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

n (%)	AU-003		GA-101	
	TN (n=22)	R/R (n=103)	TN (n=20)	R/R (n=25)
<b>ORR (PR-L or better)</b>	22 (100.0)	97 (94.2)	20 (100.0)	23 (92.0)
<b>CR/CRI</b>	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
<b>PR</b>	14 (63.6)	68 (66.0)	7 (35.0)	14 (56.0)
<b>PR or better</b>	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
<b>SD</b>	0	4 (3.9)	0	2 (8)
<b>PD</b>	0	0	0	0
<b>Discontinued prior to assessment</b>	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-19-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)
<b>COVID-19-adjusted median PFS (95% CI), mo</b>	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)
<b>COVID-19-adjusted median OS (95% CI), mo</b>	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)
<b>DOR (95% CI), mo</b>	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 naïve.

Figure 3. Kaplan-Meier Plot for COVID-19-Adjusted PFS

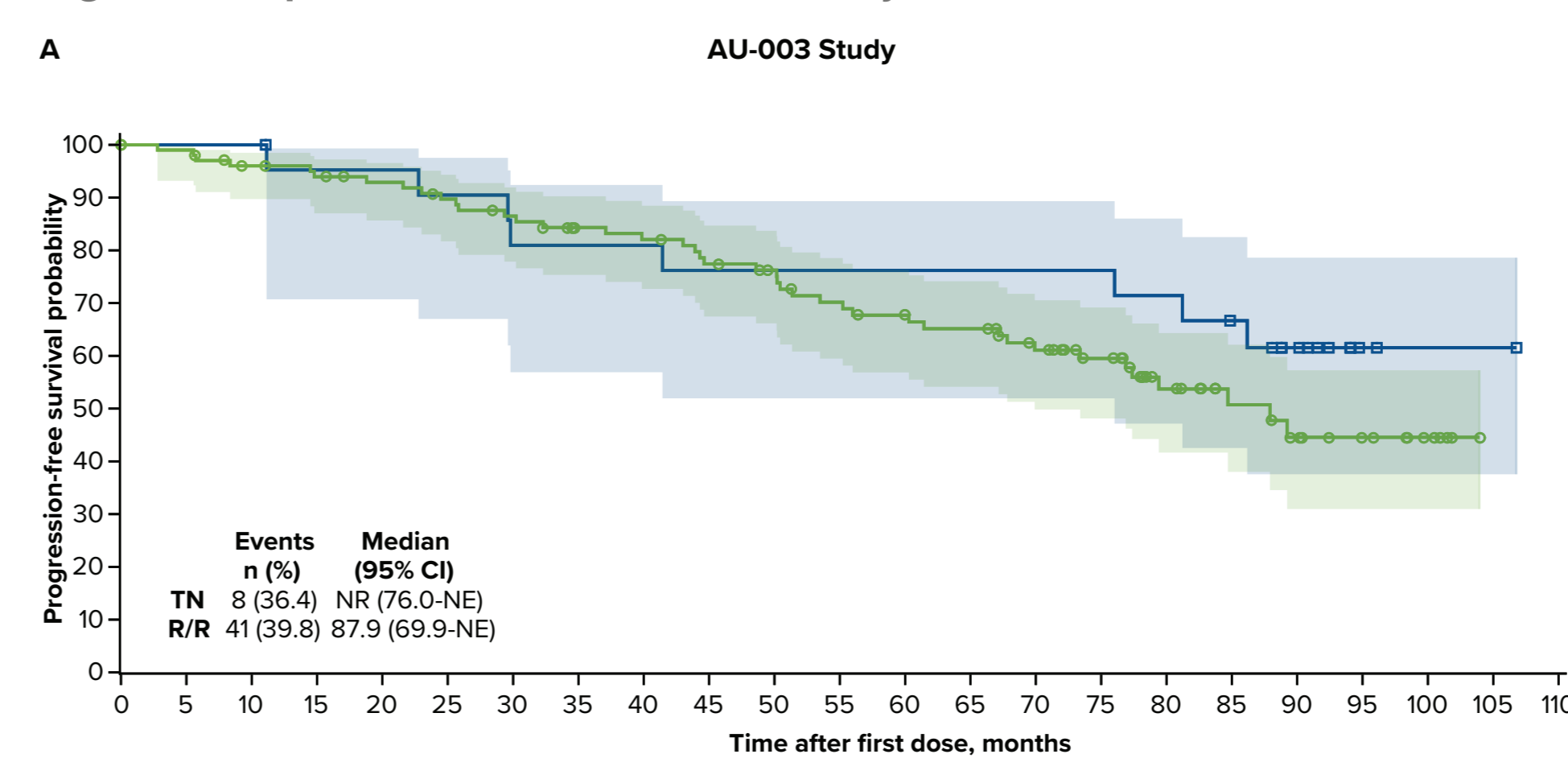
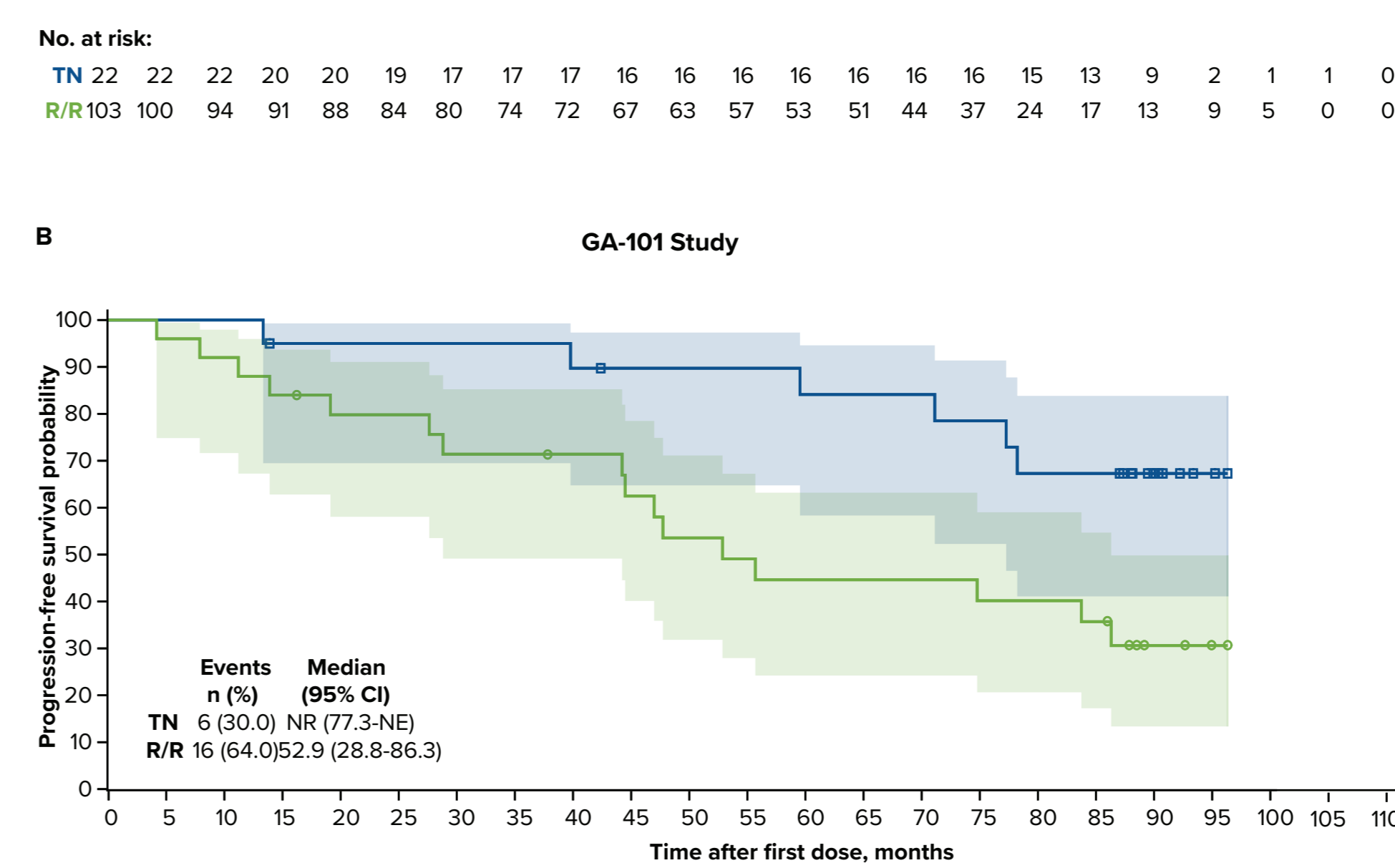
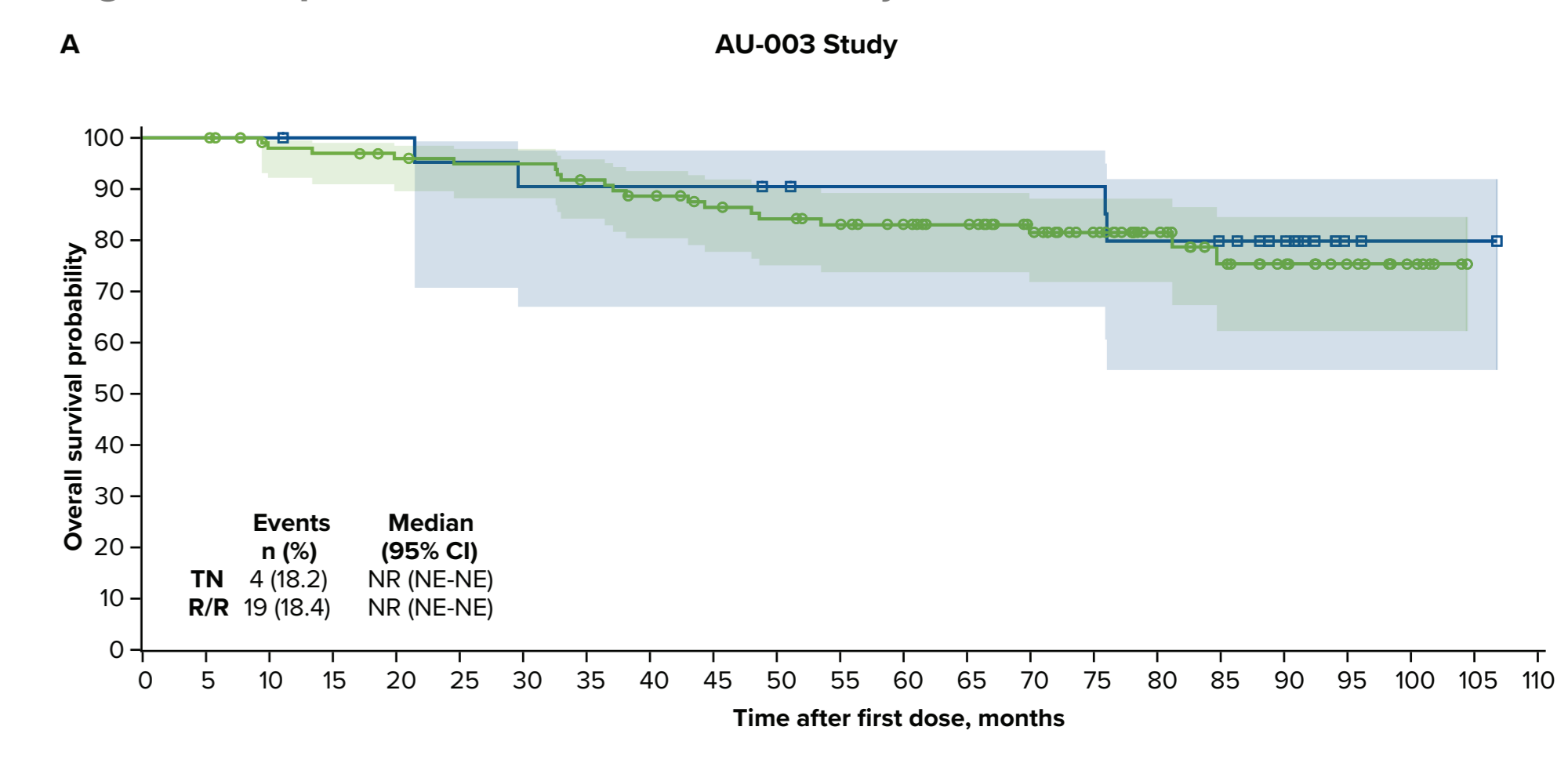


Figure 4. Kaplan-Meier Plot for COVID-19-Adjusted OS



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

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