Sonrotoclax and Zanubrutinib as Frontline Treatment for CLL Demonstrates High MRD Clearance Rates with Good Tolerability: Data from an Ongoing Phase 1/1b Study BGB-11417-101

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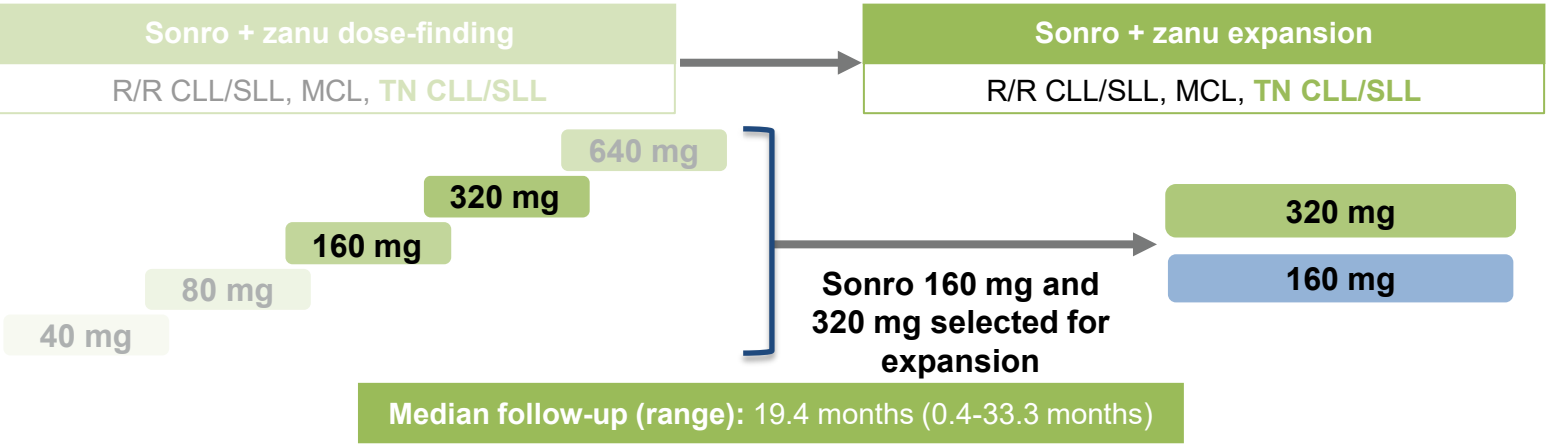
Introduction

- Ibrutinib + venetoclax in patients with CLL/SLL is effective; however, toxicities can limit use[1]
- A next-generation BCL2 inhibitor + BTK inhibitor doublet is desired to improve the safety and efficacy of combination therapy
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax with a shorter half-life and no drug accumulation[2,3]
- Zanubrutinib is highly effective in patients with TN and R/R CLL/SLL, regardless of risk factors[4,5]
  - Zanubrutinib has shown superior PFS and favorable safety/tolerability compared with ibrutinib, including fewer cardiac AEs, in patients with R/R CLL/SLL[6]
- Here, we report updated expansion data from the BGB-11417-101 trial in patients with TN CLL/SLL treated with sonrotoclax in combination with zanubrutinib

1. Kater AP, et al. *NEJM Evidence*. 2022;1(7):EVIDoa2200006; 2. Guo Y, et al. *J Med Chem*. 2024;67(10):7836-7858; 3. Liu J, et al. *Blood*. 2024;143(18):1825-1836; 4. Brukinsa (zanubrutinib). Prescribing information. BeiGene, Ltd; 2024; 5. Brukinsa (zanubrutinib). Summary of product characteristics. BeiGene, Ltd; 2021; 6. Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

BGB-11417-101 (NCT04277637) Study Design

- BGB-11417-101 is a global phase 1/1b study evaluating sonrotoclax as monotherapy, or in combination with zanubrutinib and/or obinutuzumab in patients with B-cell malignancies
- The study endpoints included safety per CTCAE v5.0, RP2D, and efficacy
- Treatment consisted of 8-12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID), then zanubrutinib + sonrotoclax until disease progression or intolerance



Baseline Characteristics

Characteristics	Sonro 160 mg + zanu (n=51)	Sonro 320 mg + zanu (n=86)	All Patients (N=137)
Study follow-up, median (range), months	19.5 (12.6-33.3)	19.3 (0.4-29.7)	19.4 (0.4-33.3)
Age, median (range), years	63 (38-82)	61 (32-84)	62 (32-84)
≥65 years, n (%)	20 (39.2)	35 (40.7)	55 (40.1)
Male sex, n (%)	37 (72.5)	61 (70.9)	98 (71.5)
Disease type, n (%)			
CLL	48 (94.1)	82 (95.3)	130 (94.9)
SLL	3 (5.9)	4 (4.7)	7 (5.1)
Risk status, n/tested (%)			
del(17p)	5/45 (11.1)	6/77 (7.8)	11/122 (9.0)
TP53 mutation[a]	11/47 (23.4)	13/62 (21.0)	24/109 (22.0)
del(11q)	10/45 (22.2)	11/77 (14.3)	21/122 (17.2)
IGHV status, n/tested (%)			
Unmutated IGHV	32/47 (68.1)	32/60 (53.3)	64/107 (59.8)
High tumor bulk[b] at baseline, n/tested (%)	22/51 (43.1)	17/82 (20.7)	39/133 (29.3)

Data cutoff: August 23, 2024.

[a] *TP53* mutations defined as >0.1% VAF. [b] Nodes ≥10 cm or nodes >5 cm and ALC >25×10^9/L.

Sonrotoclax in Combination with Zanubrutinib is Well Tolerated With Low Treatment Discontinuation Rates

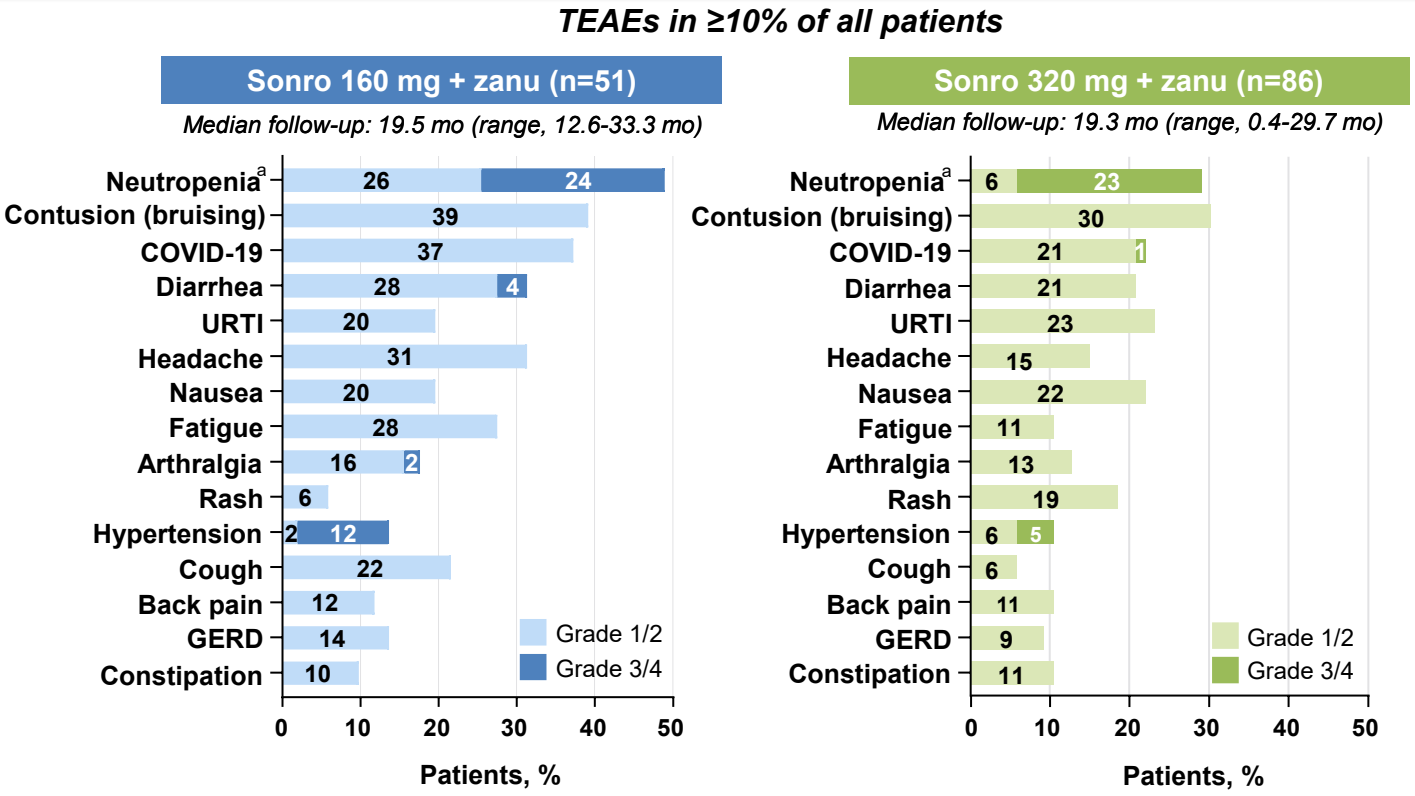
Patients, n (%)	Sonro 160 mg + zanu (n=51)	Sonro 320 mg + zanu (n=86)	All Patients (N=137)
Duration of exposure, median (range), months	18.7 (5.8-33.3)	19.3 (0.4-29.7)	19.2 (0.4-33.3)
Any TEAEs	51 (100)	77 (89.5)	128 (93.4)
Grade ≥3	29 (56.9)	39 (45.3)	68 (49.6)
Serious TEAEs	13 (25.5)	20 (23.3)	33 (24.1)
Leading to death	0	0	0
Leading to discontinuation of zanu	1 (2)	4 (4.7)	5 (3.6)[a,b]
Treated with sonro	51 (100)	67 (77.9)	118 (86.1)
Leading to discontinuation of sonro	1 (2)	2 (2.3)	3 (2.2)[a]
Relative dose intensity of sonro, median, %	98.9	99.0	99.0

- As of the data cutoff date, 19 patients in the 320-mg cohort remained in zanubrutinib lead-in

[a] Three discontinuations of sonro + zanu (n=1 each): meningitis (sonro 160 mg on study day 177), CMML (sonro 320 mg on study day 742), recurrent sinusitis (sonro 320 mg on study day 533).
[b] Two discontinuations of zanu only (n=1 each): intracranial hemorrhage (study day 318), intermittent diarrhea (grade 1 on study day 30).

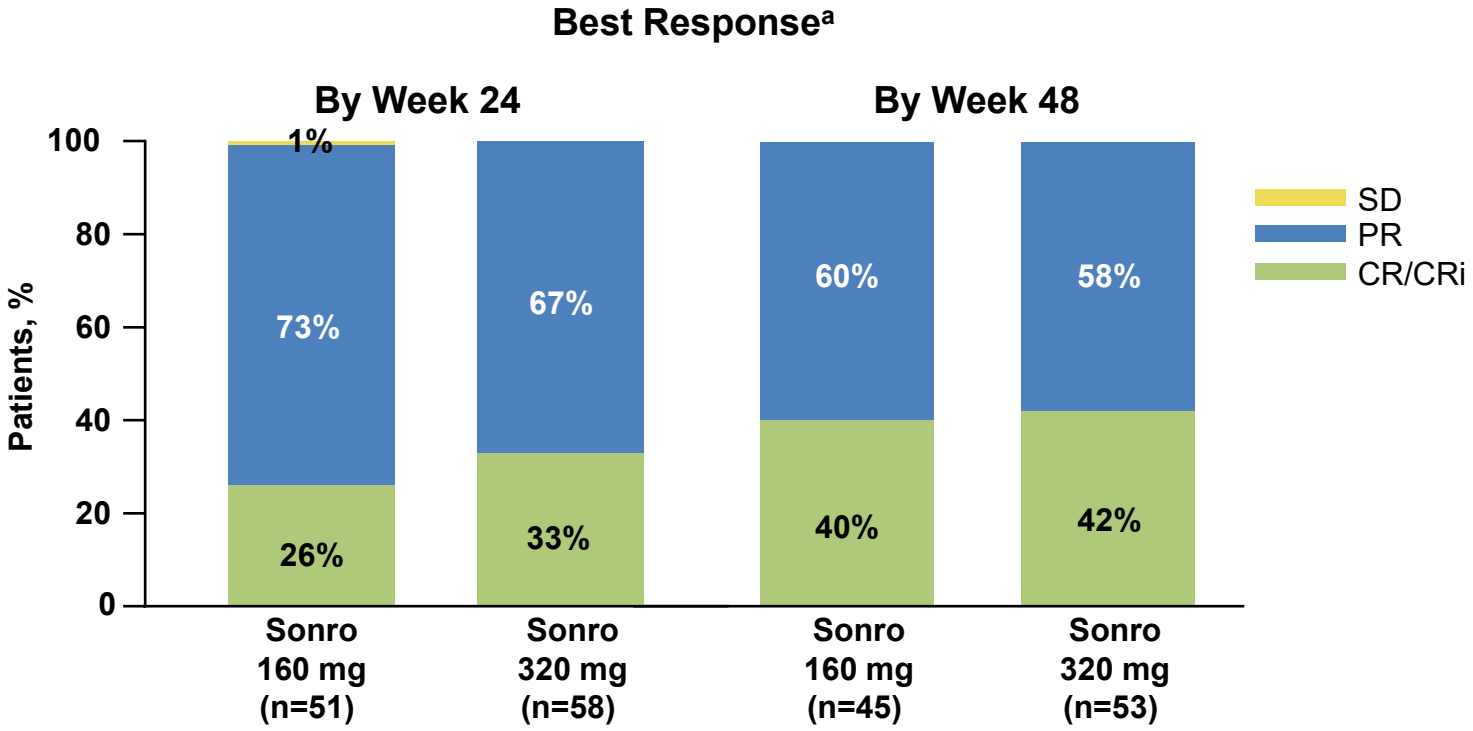
TEAEs Observed With Sonrotoclax + Zanubrutinib Were Mostly Low Grade and Transient

- No TLS
- Neutropenia was transient and did not lead to higher rates of grade ≥3 infections



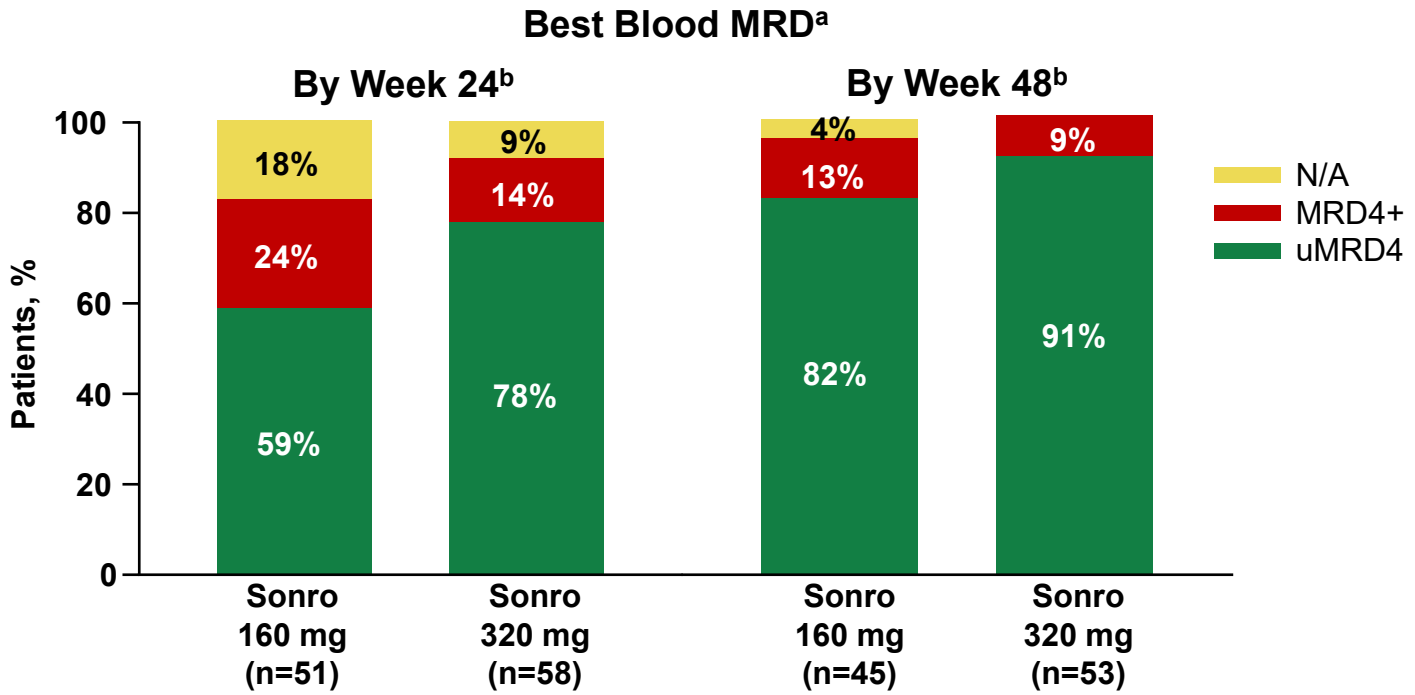
[a] Includes the combined preferred terms *neutrophil count decreased* and *neutropenia*.

Sonrotoclax + Zanubrutinib Demonstrates Substantial Antitumor Activity in TN CLL



[a] Percentages based on the number of patients who reached assessment at 24 or 48 weeks after completion of ramp-up, following zanu monotherapy and sonro ramp-up to target dose.

High Blood uMRD4 Rates Occurred Early and All Patients Remain in uMRD

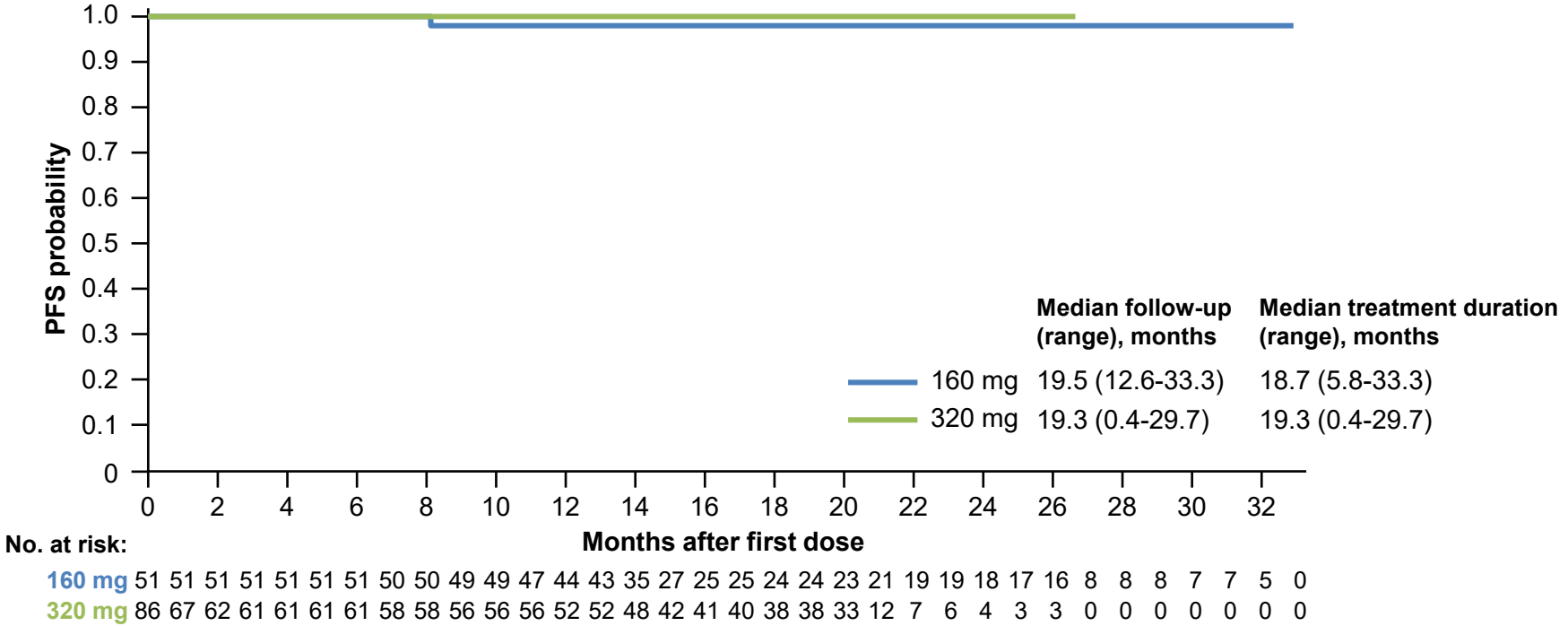


- As of the data cutoff date, no patients had switched from uMRD to MRD4+

[a] As measured by ERIC flow cytometry panel; uMRD4 is defined as less than 1 CLL cell per 10,000 leukocytes ($<10^{-4}$). [b] Number of weeks at target dose, following zanu monotherapy and sonro ramp-up to target dose.

At Median Study Follow-Up of 19.4 Months, No Progression Was Observed With Sonrotoclax 320 mg

- 1 PFS event in sonrotoclax 160-mg cohort (Richter transformation)



With Longer Follow-Up, Sonrotoclax + Zanubrutinib Continued to Demonstrate Compelling Safety and Efficacy in TN CLL

- Sonrotoclax 160 or 320 mg in combination with zanubrutinib (320 mg) was generally safe and well tolerated, with a median relative dose intensity of 99%
  - No laboratory or clinical TLS occurred
  - Majority of TEAEs were low grade; low rates of GI TEAEs, predominantly grade 1, were observed
  - The most common grade ≥3 TEAE was neutropenia, which was mostly transitory
  - No fatal TEAEs, no complicated COVID-19 case or death
- Substantial efficacy was observed in this all-comer TN CLL/SLL population, including in patients with high-risk features
  - The sonrotoclax + zanubrutinib combination demonstrated a high response rate, including 100% ORR in the 320-mg cohort
  - High and early blood uMRD4 was seen by week 24 of combination therapy in both dose cohorts, with higher rates in the 320-mg cohort and further deepening by week 48 in both cohorts. No patient has progressed from uMRD4 to MRD4+
  - With median follow-up of 19.4 months, only 1 primary progression occurred in the 160-mg cohort that was an RT
- Sonrotoclax 320 mg in combination with zanubrutinib is being evaluated in patients with TN CLL in the phase 3 study, CELESTIAL-TNCLL (NCT06073821)

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