Sonrotoclax + Zanubrutinib for TN-CLL Demonstrates MRD Clearance and Tolerability in Ongoing Phase 1/1b Study (BGB-11417-101)

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Piers E.M. Patten,[1,2] Jacob D. Soumerai,[3] Chan Y. Cheah,[4-6] Stephen S. Opat,[7] Raul Cordoba,[8] Paolo Ghia,[9,10] Sheel Patel,[11] Yiqian Fang,[12] Wei Ding,[11] Constantine S. Tam[13]

[1]Comprehensive Cancer Centre, King's College London, London, UK; [2]King's College Hospital, London, UK; [3]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [4]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [5]Medical School, University of Western Australia, Crawley, WA, Australia; [6]Linear Clinical Research, Nedlands, WA, Australia; [7]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [8]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [9]Università Vita-Salute San Raffaele, Milano, Italy; [10]IRCCS Ospedale San Raffaele, Milano, Italy; [11]BeiGene USA, Inc, San Mateo, CA, USA; [12]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [13]Alfred Hospital and Monash University, Melbourne, VIC, Australia

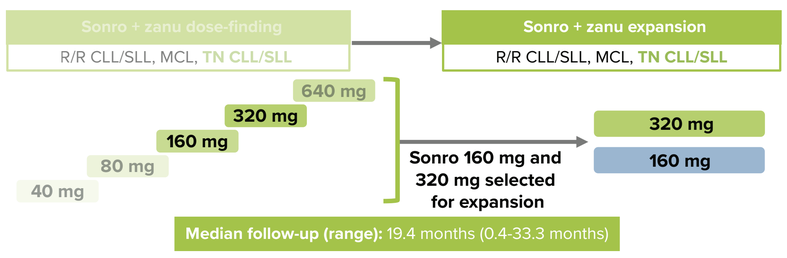
INTRODUCTION

- Ibrutinib + venetoclax in patients with chronic lymphocytic leukemia (CLL)/ small lymphocytic lymphoma (SLL) is effective; however, toxicities can limit use[1]
- A next-generation BCL2 inhibitor + Bruton tyrosine kinase (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 treatment naive (TN) and relapsed/refractory (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

METHODS

- BGB-11417-101 (NCT04277637) 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 (**Figure 1**)

Figure 1. BGB-11417-101 Study Design



RESULTS

Disposition

- As of August 23, 2024, 137 patients were enrolled
  - Patient and disease characteristics are shown in **Table 1**

Table 1. Baseline Demographics and Clinical 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.

Safety

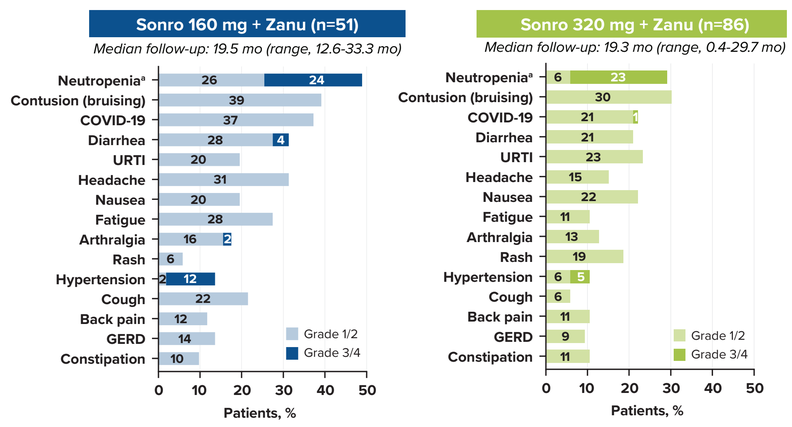
- Three patients discontinued combination treatment, while 2 discontinued zanubrutinib only (**Table 2**)
- As of the data cutoff date, 19 patients in the 320-mg cohort remained in zanubrutinib lead-in
- The most common TEAEs for all patients were neutropenia (160 mg, 49%; 320 mg, 29%), contusion (160 mg, 39%; 320 mg, 30%), COVID-19 (160 mg, 37%; 320 mg, 22%), and diarrhea (160 mg, 31%; 320 mg, 21%)
  - Neutropenia was the most common grade ≥3 TEAE (**Figure 2**)
  - Neutropenia was transient and did not lead to higher rates of grade ≥3 infections
- No tumor lysis syndrome (TLS) or deaths occurred

Table 2. Overall Safety Summary

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

[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).

Figure 2. Most Common TEAEs (≥10% of All Patients)

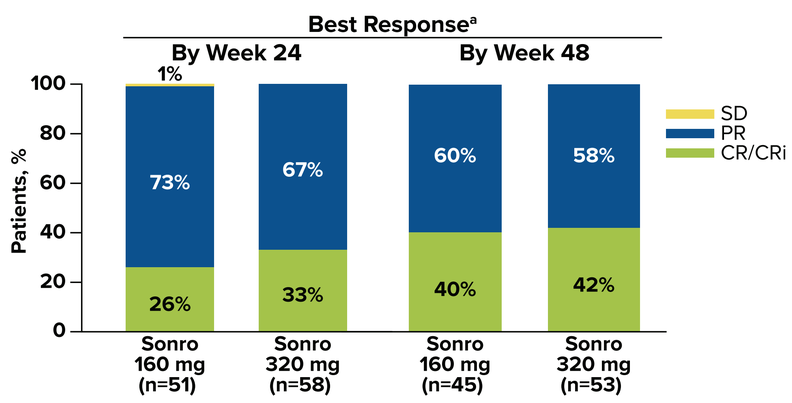


[a] Includes the combined preferred terms *neutrophil count decreased* and *neutropenia*.
GERD, gastroesophageal reflux disease; URTI, upper respiratory tract infection.

Efficacy

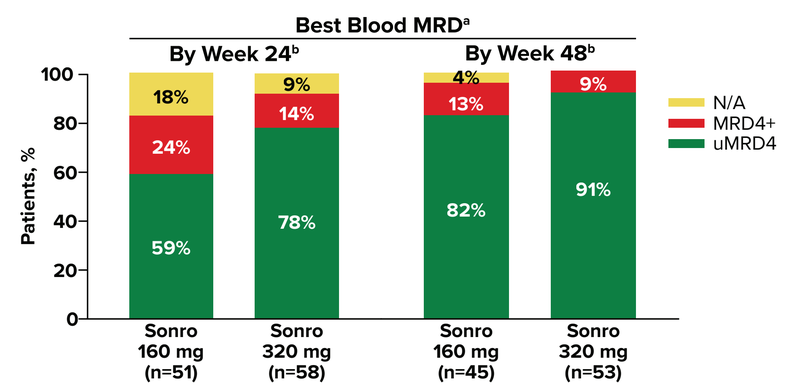
- In efficacy-evaluable patients, the CR/CRi rates by week 24 were 26% and 33%, and by week 48 were 40% and 42% for the 160-mg and 320-mg cohorts, respectively (**Figure 3**)
- Best blood uMRD4 rates by week 24 were 59% and 78%, and by week 48 were 82% and 91% for the 160-mg and 320-mg cohorts, respectively (**Figure 4**)
  - As of the data cutoff date, no patients had switched from uMRD4 to MRD4+
- One PFS event occurred in the 160-mg cohort (Richter transformation); no progression was seen in the 320-mg cohort (**Figure 5**)

Figure 3. Best Response Rates by Weeks 24 and 48



[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.

Figure 4. Best Blood MRDs by Weeks 24 and 28

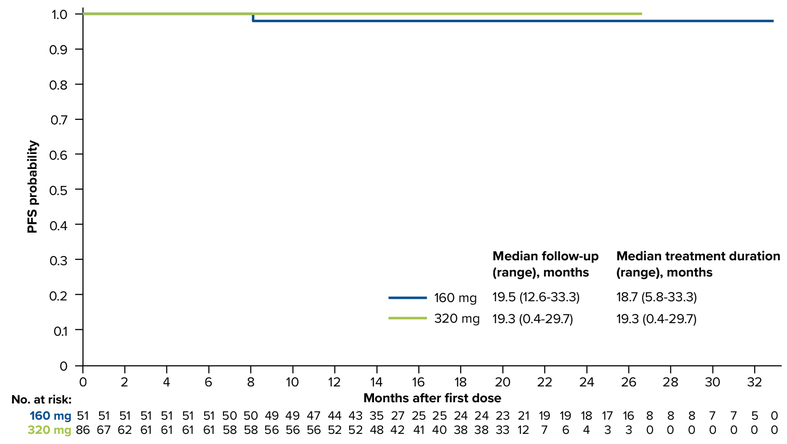


[a] As measured by ERIC flow cytometry panel; uMRD4 is defined as less than 1 CLL cell per 10,000 leukocytes (<10^{-4}).
[b] Number of weeks at target dose, following zanu monotherapy and sonro ramp-up to target dose.

CONCLUSIONS

- 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 gastrointestinal TEAEs, predominantly grade 1, were observed
  - The most common grade ≥3 TEAE was neutropenia, which was mostly transitory
  - No fatal TEAEs and no complicated COVID-19 case or death occurred
- 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 Richter transformation
- Sonrotoclax 320 mg in combination with zanubrutinib is being evaluated in patients with TN CLL in the phase 3 study, CELESTIAL-TNCLL (NCT06073821)

Figure 5. PFS for Sonrotoclax + Zanubrutinib



REFERENCES

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.

DISCLOSURES

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CORRESPONDENCE: Piers E.M. Patten, piers.patten1@nhs.net

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