Results From the Phase 1 Study of the Novel BCL2 Inhibitor Sonrotoclax in Combination With Zanubrutinib for Relapsed/Refractory CLL/SLL Show Deep and Durable Responses

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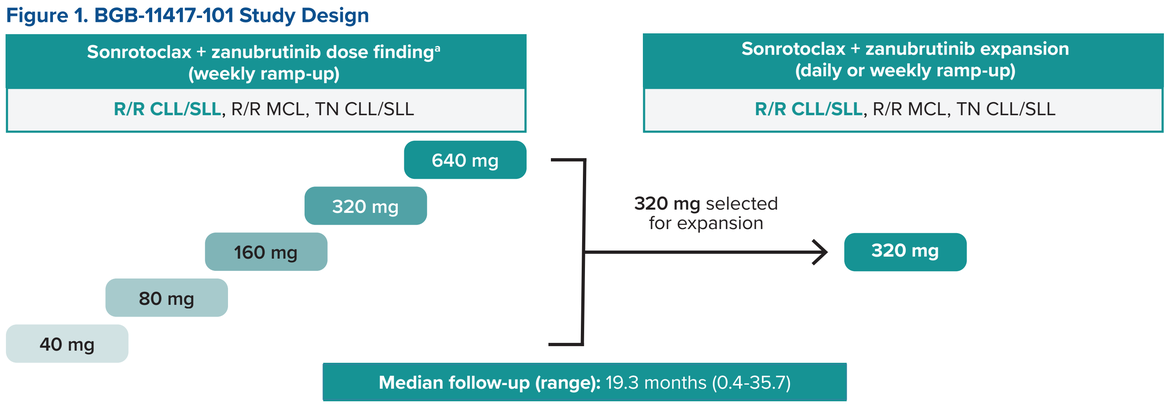
INTRODUCTION

- CLL/SLL remains incurable as many treated patients experience relapse,[1] necessitating further treatment with novel agents
- 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]
- Zanubrutinib is a next-generation BTK inhibitor approved globally for 5 indications, including CLL[3,4]
  - Zanubrutinib has shown superior PFS and safety/tolerability compared with ibrutinib, including fewer cardiac AEs, in patients with R/R CLL/SLL[5]
- Here, updated safety and efficacy data are presented for patients with R/R CLL/SLL treated with sonrotoclax + zanubrutinib in the ongoing BGB-11417-101 study (NCT04277637)

METHODS

- BGB-11417-101 is a global phase 1/1b study evaluating sonrotoclax as monotherapy, or in combination ± zanubrutinib, and ± obinutuzumab in patients with B-cell malignancies (**Figure 1**)
- The primary endpoints were safety per CTCAE v5.0, MTD, and RP2D
- Treatment consisted of 8-12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID), then in combination with sonrotoclax (with weekly or daily ramp-up to target dose) until PD

Figure 1. BGB-11417-101 Study Design



[a]The safety monitoring committee reviewed dose-level cohort data before dose escalation.

RESULTS

Table 1. Baseline Patient Characteristics

Characteristic	Sonro 40 mg + Zanu (n=4)	Sonro 80 mg + Zanu (n=9)	Sonro 160 mg + Zanu (n=6)	Sonro 320 mg + Zanu (n=22)	Sonro 640 mg + Zanu (n=6)	All (N=47)
Study follow-up, median (range), months	34.0 (10.2-35.7)	27.7 (10.0-34.5)	29.2 (28.3-30.8)	6.8 (0.4-26.9)	18.1 (10.9-22.6)	19.3 (0.4-35.7)
Age, median (range), years	60 (50-71)	62 (55-75)	62 (41-76)	67 (36-76)	60 (53-69)	65 (36-76)
Male sex, n (%)	4 (100)	8 (89)	3 (50)	18 (82)	2 (33)	35 (75)
ECOG PS, n (%)						
0	4 (100)	5 (56)	4 (67)	11 (50)	4 (67)	28 (60)
1	0	3 (33)	2 (33)	10 (46)	2 (33)	17 (36)
Risk status, n/tested (%)[a]						
del(17p)	3/4 (75)	4/8 (50)	1/6 (17)	3/18 (17)	0	11/42 (26)
del(17p) and/or *TP53* mutation	**3/4 (75)**	**7/9 (78)**	**2/6 (33)**	**13/22 (59)**	**0**	**25/47 (53)**
IGHV status, n/tested (%)						
Unmutated	**1/3 (33)**	**6/6 (100)**	**3/6 (50)**	**3/4 (75)**	**0**	**13/19 (68)**
Prior therapy						
No. of lines of prior therapy, median (range)	1.5 (1-2)	1 (1-2)	1 (1-2)	1 (1-3)	1 (1-1)	1 (1-3)
Prior BTK inhibitor, n (%)[b]	**1 (25)**	**1 (11)**	**1 (17)**	**3 (14)**	**1 (17)**	**7 (15)**
Prior BTK inhibitor duration, median (range), months	86.6 (86.6-86.6)	1.6 (1.6-1.6)	18.5 (18.5-18.5)	38.1 (34.2-49.1)	24.0 (24.0-24.0)	34.2 (1.6-86.6)

Data cutoff: February 4, 2024.
[a] *TP53* mutations defined as >0.1% variant allele frequency. [b]BTK inhibitor was the last prior therapy for 7 patients: all discontinued due to toxicity.

- No DLTs occurred and MTD was not reached; the 320-mg sonrotoclax + zanubrutinib cohort was expanded as RP2D
- Sonrotoclax in combination with zanubrutinib was well tolerated, with very low rates of treatment discontinuation and dose reductions; no deaths were observed (**Table 2**)

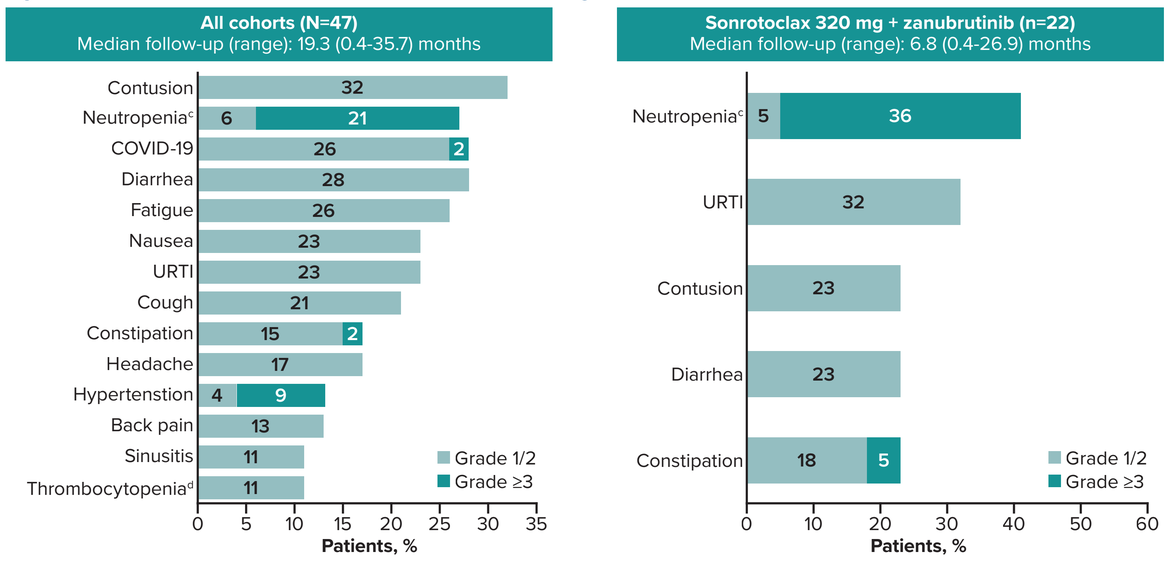
Table 2. TEAE Summary

Patients, n (%)	Sonro 40 mg + Zanu (n=4)	Sonro 80 mg + Zanu (n=9)	Sonro 160 mg + Zanu (n=6)	Sonro 320 mg + Zanu (n=22)	Sonro 640 mg + Zanu (n=6)	All (N=47)
Any TEAEs	4 (100)	9 (100)	6 (100)	20 (91)	5 (83)	44 (94)
Grade ≥3	1 (25)	5 (56)	3 (50)	13 (59)	2 (33)	24 (51)
Serious TEAEs	1 (25)	1 (11)	3 (50)	7 (32)	1 (17)	13 (28)
Led to zanu discontinuation	0	1 (11)[a]	0	0	1 (17)[c]	2 (4)
Led to zanu dose reduction	0	0	0	1 (4.5)[b]	0	1 (2)
Treated with sonro, n (%)	4 (100)	9 (100)	6 (100)	19 (86)[d]	6 (100)	44 (94)
TEAEs leading to sonro discontinuation	0	0	0	0	1 (17)[c]	1 (2)
TEAEs leading to sonro dose reduction	0	0	0	0	0	0

[a]Grade is listed as worst grade experienced by patient on any drug. [b]Hematologic AEs were graded per iwCLL criteria; nonhematologic AEs were graded per CTCAE v5.0 criteria.
[c]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [d]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

- TEAEs observed with sonrotoclax + zanubrutinib were mostly low grade and transient (**Figure 2**)
  - No cases of TLS, atrial fibrillation, or febrile neutropenia occurred
  - No patients had dose reductions due to diarrhea

Figure 2. TEAEs in ≥5 Patients and at Sonrotoclax RP2D of 320 mg[a,b]



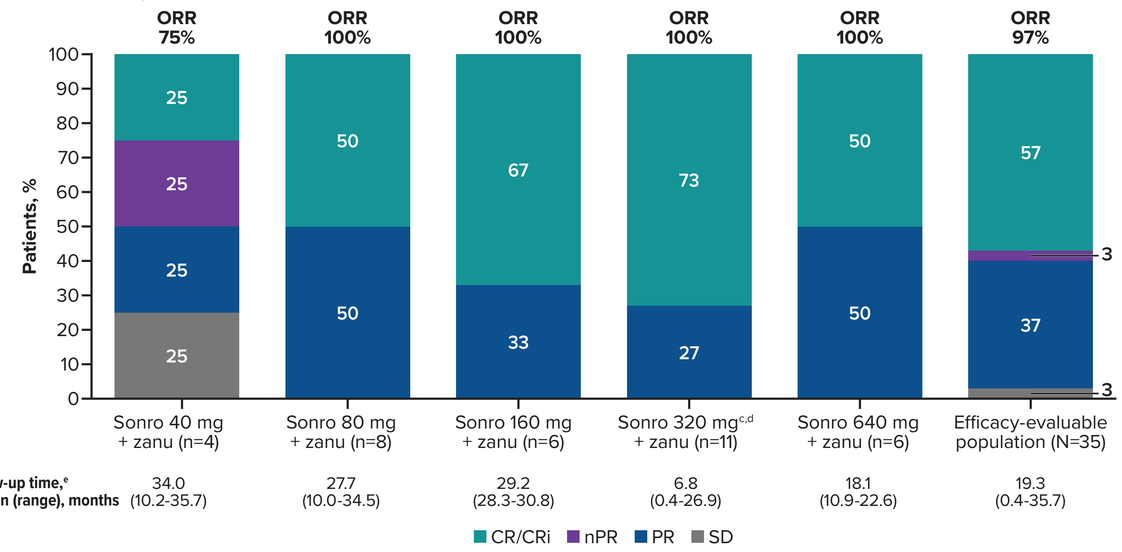
[a]Grade is listed as worst grade experienced by patient on any drug. [b]Hematologic AEs were graded per iwCLL criteria; nonhematologic AEs were graded per CTCAE v5.0 criteria.
[c]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [d]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

CONCLUSIONS

- Sonrotoclax + zanubrutinib combination treatment had a tolerable safety profile in patients with R/R CLL/SLL at all dose levels tested up to 640 mg
  - 46/47 of patients remain on study treatment with a median follow-up of 19.3 months
  - No TLS and no cardiac toxicity, including atrial fibrillation, were observed
  - The most commonly reported hematologic TEAE was neutropenia, which was mostly transitory, with no cases of febrile neutropenia, and did not require sonrotoclax dose reductions
- Efficacy was promising in this R/R CLL/SLL population, including patients with high-risk features
  - The combination of sonrotoclax + zanubrutinib demonstrated a 97% ORR, with a CR/CRi rate of 57% across all dose levels and 100% ORR with a CR/CRi rate of 73% at 320 mg
  - Responses deepened over time with high blood MRD negativity observed by week 48 of combination therapy
  - At 19.3 months of median study follow-up, only 1 PFS event occurred in the lowest tested dose (40 mg)
- Follow-up is ongoing with this promising combination therapy

- With a median study follow-up of 19.3 months, the ORR was 97%, with a 57% CR/CRi rate across all doses (**Figure 3**)
  - In the 320-mg cohort, the ORR was 100%, with a 73% CR/CRi rate
- The median time to CR or CRi was 9.8 months (range, 5.3-22.8 months)
- Of 6 evaluable patients with prior BTK inhibitor therapy, 4 achieved PR and 1 achieved CR

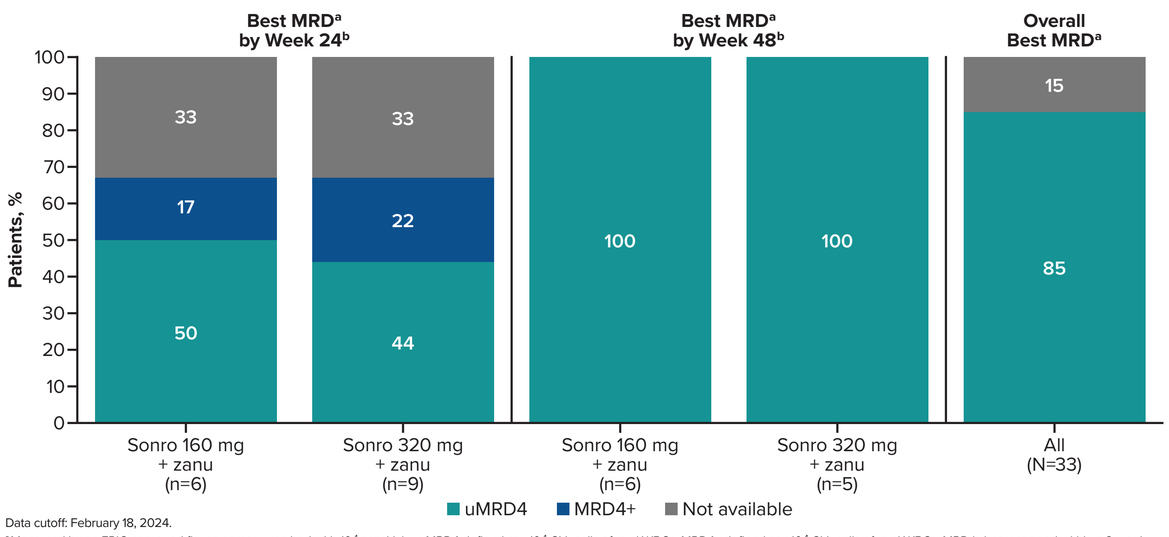
Figure 3. Overall Response Rates[a,b]



[a]Responses were assessed per 2008 iwCLL criteria and percentage of response is based on number of patients who had at least 1 post-baseline tumor assessment after dosing sonrotoclax. [b]ORR was defined as PR-L or better. [c]One patient achieved CRi. [d]One patient previously exposed to venetoclax was included and achieved CR. [e]For all patients as treated (n=47).

- Of 33 MRD-evaluable patients, 28 (85%) had uMRD at time of data cutoff (**Figure 4**)
- Data shows evidence of responses deepening over time
- All patients in the 160-mg, 320-mg, and 640-mg cohorts who reached week 48 achieved uMRD

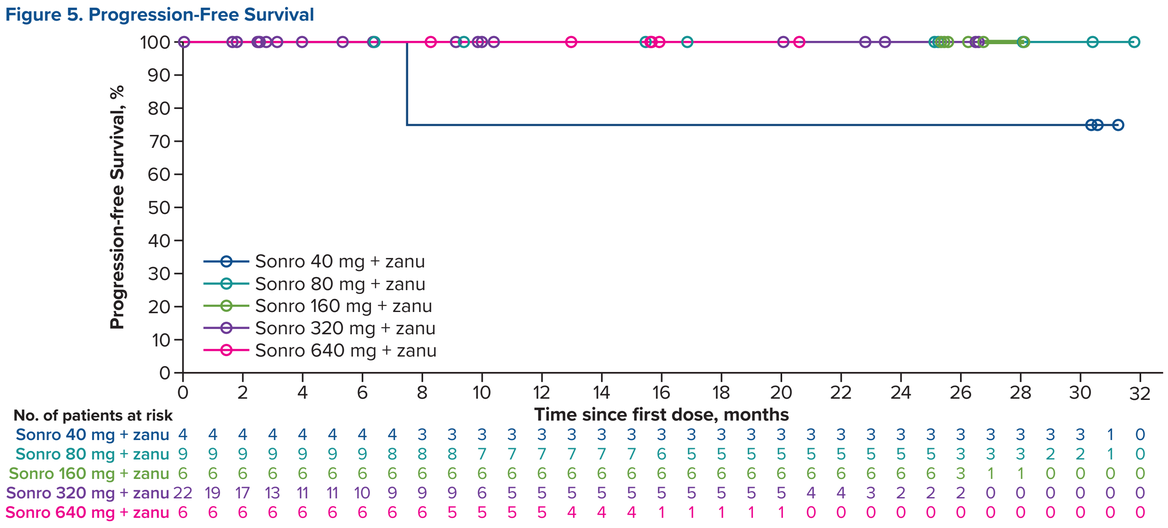
Figure 4. Best MRD in Peripheral Blood



Data cutoff: February 18, 2024.
[a]Measured by an ERIC-approved flow cytometry method with 10^{-4} sensitivity. uMRD4 defined as $<10^{-4}$ CLL cells of total WBCs. MRD4+ defined as $\geq 10^{-4}$ CLL cells of total WBCs. MRD is best reported within a 2-week window following the week 24/week 48 day 1 MRD assessments. [b]Week 24 or 48 of treatment at target dose, following zanubrutinib monotherapy and sonrotoclax ramp-up to target dose.

- With a median study follow-up of 19.3 months, only 1 PFS event occurred in the 40-mg cohort (**Figure 5**)

Figure 5. Progression-Free Survival



REFERENCES

1. Hillmen P, et al. *J Clin Oncol.* 2019;37(30):2722-2729.
2. Hu N, et al. AACR 2020. Abstract 3077.
3. Brukinsa. Prescribing information. BeiGene, Ltd; 2024.
4. Brukinsa. Summary of product characteristics. BeiGene, Ltd; 2021.
5. Brown JR, et al. *N Engl J Med.* 2023;388(4):319-332.

DISCLOSURES

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