Sonrotoclax Monotherapy for Treatment of Patients With Relapsed/Refractory CLL: Data From an Ongoing Phase 1/1b Study (BGB-11417-101)

PF580

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CONCLUSIONS

- Sonrotoclax monotherapy had a tolerable patient safety profile across all doses tested and demonstrated substantial antitumor activity in a heavily pretreated, high-risk cohort of patients with R/R CLL/SLL, most of whom received prior BTK inhibitors
  - No clinical TLS events were reported
  - Sonrotoclax treatment led to deep and durable responses, and median PFS was not reached after a median follow-up of 24.7 months
  - In the 320-mg cohort, the ORR was 100%, the best uMRD rate was 100%, no PFS events had occurred, and all patients remain on treatment as of the data cutoff date
- Based on these results, sonrotoclax 320 mg was selected as the RP2D and is being tested as monotherapy or in combinations in potential registrational studies

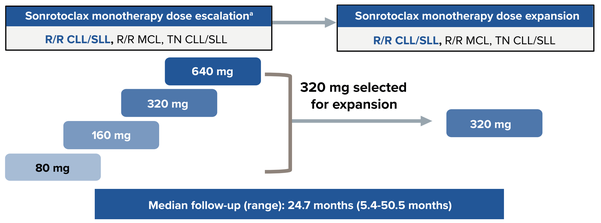
INTRODUCTION

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) remains incurable as many patients experience relapse,[1] necessitating further treatment with novel agents
- Sonrotoclax (BGB-11417), a next-generation B-cell lymphoma 2 (BCL2) inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation[2]
- Here, updated safety and efficacy data are presented for patients with relapsed/refractory (R/R) CLL/SLL treated with sonrotoclax monotherapy in the ongoing BGB-11417-101 study

METHODS

- BGB-11417-101 (NCT04277637) is an ongoing phase 1/1b, open-label, multicenter, dose-escalation and -expansion study of sonrotoclax as monotherapy or in combination with zanubrutinib or obinutuzumab in patients with various B-cell malignancies (**Figure 1**)
- Eligible patients have CLL/SLL that requires treatment and has relapsed after or was refractory to at least 1 prior line of therapy
- Sonrotoclax is administered orally once daily, with ramp-up to the intended target dose to prevent tumor lysis syndrome (TLS), until disease progression or unacceptable toxicity
- The primary study objectives are to assess safety/tolerability, define the maximum tolerable dose (MTD), and determine the recommended phase 2 dose (RP2D) of sonrotoclax monotherapy; a secondary objective is to assess the overall response rate (ORR) per iwCLL 2018 criteria[3]
- Exploratory endpoints include assessment of measurable residual disease in blood by ERIC flow cytometry assay at week 12 and then every 24 weeks thereafter

Figure 1. BGB-11417-101 Study Design



[a]The safety monitoring committee reviewed dose-level cohort data before dose escalation.
Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; R/R, relapsed/refractory; TN, treatment naive.

RESULTS

- As of March 1, 2025, 18 patients with R/R CLL/SLL had received sonrotoclax monotherapy, and 12 (66.7%) remain on treatment
  - Six patients (33.3%) discontinued treatment due to progressive disease (n=3), physician decision (n=2), or patient withdrawal (n=1)
- Across dose cohorts, the median age was 68.0 years and the median number of prior systemic treatments was 3 (**Table 1**)
  - Among tested patients, 93.3% (14/15) had unmutated IGHV, 28.6% (4/14) had del(17p), and 58.3% (7/12) had del(17p) and/or *TP53* mutation
  - Of the 18 patients, 17 had received prior Bruton tyrosine kinase (BTK) inhibitor treatment

Table 1. Baseline Patient Characteristics

Characteristic	Sonrotoclax 80 mg (n=4)	Sonrotoclax 160 mg (n=7)	Sonrotoclax 320 mg (n=7)	All (N=18)
Follow-up, median (range), months	45.2 (44.0-50.5)	23.2 (5.4-42.7)	22.7 (14.6-28.1)	24.7 (5.4-50.5)
Age, median (range), years	65.5 (55-70)	73.0 (61-84)	65.0 (62-79)	68.0 (55-84)
Male, n (%)	4 (100)	3 (42.9)	5 (71.4)	12 (66.7)
ECOG PS, n (%)				
0	2 (50.0)	3 (42.9)	3 (42.9)	8 (44.4)
1	2 (50.0)	4 (57.1)	4 (57.1)	10 (55.6)
del(17p), n/tested (%)	1/3 (33.3)	1/6 (16.7)	2/5 (40.0)	4/14 (28.6)
del(17p) and/or *TP53* mutation, n/tested (%)	1/2 (50.0)	3/6 (50.0)	3/4 (75.0)	7/12 (58.3)
Unmutated IGHV, n/tested (%)	2/2 (100)	5/6 (83.3)	7/7 (100)	14/15 (93.3)
Prior therapy				
No. of lines of prior systemic therapy, median (range)	2.5 (1-3)	2.0 (1-4)	4.0 (1-5)	3.0 (1-5)
No. of lines of prior systemic therapy, n (%)				
1	1 (25.0)	1 (14.3)	1 (14.3)	3 (16.7)
2	1 (25.0)	3 (42.9)	1 (14.3)	5 (27.8)
≥3	2 (50.0)	3 (42.9)	5 (71.4)	10 (55.6)
Prior BTK inhibitor, n (%)	3 (75.0)	7 (100)	7 (100)	17 (94.4)
Prior BTK inhibitor duration, median (range), months	47.0 (40.9-53.7)	59.6 (33.8-87.3)	78.5 (24.5-113.0)	61.0 (24.5-113.0)

Abbreviations: BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region.

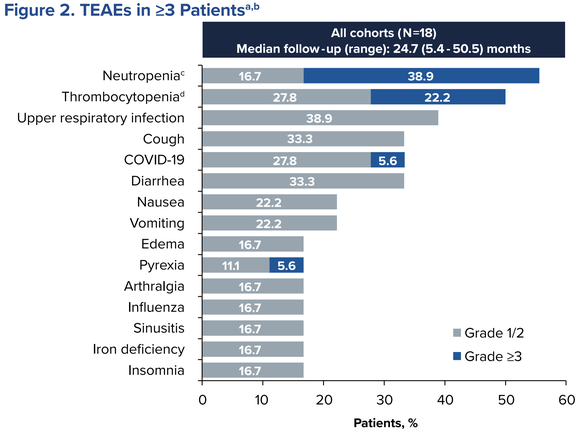
- An overall summary of treatment-emergent adverse events (TEAEs) is shown in **Table 2**
  - No patients died due to TEAE or discontinued sonrotoclax due to TEAE
- Toxicity was generally the same among all tested dose levels with no new safety signals identified; the sonrotoclax 320 mg dose level was chosen for expansion
- Across all dose cohorts, the most common any-grade TEAEs were neutropenia (55.6%), thrombocytopenia (50.0%), and upper respiratory infection (38.9%); neutropenia was the most common grade ≥3 TEAE (**Figure 2**)
  - Neutropenia was manageable and did not lead to a higher rate of grade ≥3 infections; eight patients used granulocyte-colony stimulating factor
- Two patients (11.1%; n=1 each in 80-mg and 320-mg cohorts) experienced laboratory TLS during sonrotoclax ramp-up; both events resolved within 24 hours without sequelae or dose modification
- While MTD was not reached at 320 mg, the 640-mg dose was not tested in this cohort

Table 2. TEAE Summary

Patients, n (%)	Sonrotoclax 80 mg (n=4)	Sonrotoclax 160 mg (n=7)	Sonrotoclax 320 mg (n=7)	All (N=18)
Any TEAEs	4 (100)	7 (100)	7 (100)	18 (100)
Grade ≥3	2 (50.0)	6 (85.7)	6 (85.7)	14 (77.8)
Serious	3 (75.0)	3 (42.9)	3 (42.9)	9 (50.0)
Led to sonrotoclax discontinuation	0	0	0	0
Led to sonrotoclax dose interruption	3 (75.0)	5 (71.4)	2 (28.6)	10 (55.6)
Led to sonrotoclax dose reduction	0	2 (28.6)[a]	1 (14.3)[b]	3 (16.7)

[a]Grade ≤2 diarrhea (n=2). [b]Grade 2 platelet count decreased (n=1).
Abbreviation: TEAE, treatment-emergent adverse event.

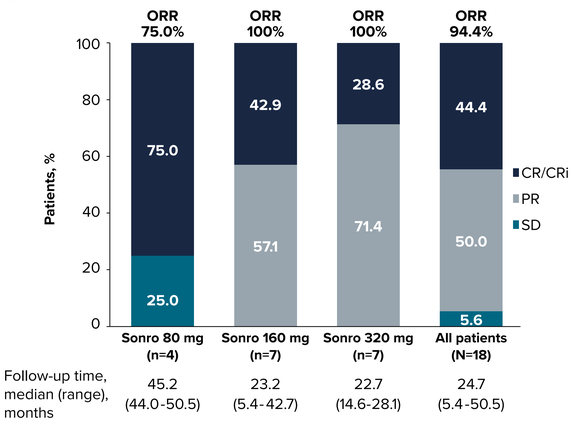
Figure 2. TEAEs in ≥3 Patients[a,b]



[a]Grade is listed as worst grade experienced by the patient on any drug. [b]Hematologic TEAEs were graded per iwCLL criteria; nonhematologic TEAEs 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*.
Abbreviation: TEAE, treatment-emergent adverse event.

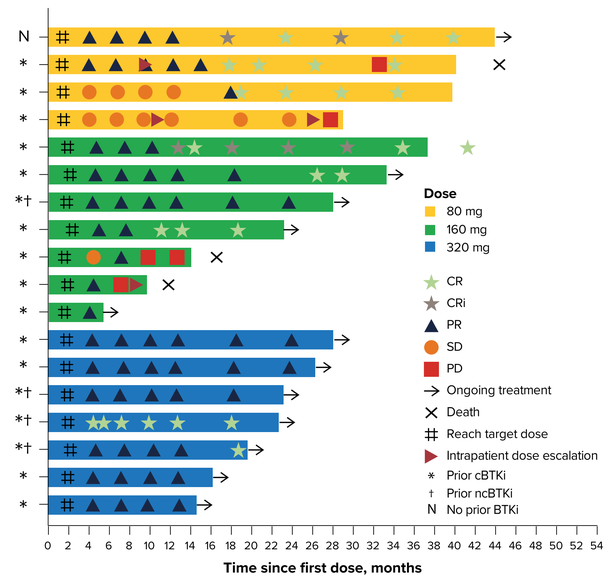
- With a median study follow-up of 24.7 months, the ORR was 94.4% across all dose cohorts (**Figures 3** and **4**)
  - Complete responses (CRs) were seen in 44.4% of patients, with a median time to CR of 17.8 months (range, 4.4-26.5 months)
  - Median duration of response has not yet been reached
- In the 320-mg cohort, the ORR was 100% with a median 22.7 months of study follow-up
  - CRs were seen in 28.6% of patients, with a median time to CR of 11.6 months (range, 4.4-18.7 months)
- Median progression-free survival (PFS) was not reached after a median follow-up of 23.7 months (range, 4.0-41.2 months)
  - No PFS events occurred in the 320-mg cohort and all patients remain on treatment
- The best undetectable measurable residual disease rate was 75% across all patients and 100% in the 320-mg cohort (**Figure 5**)

Figure 3. Response Rates



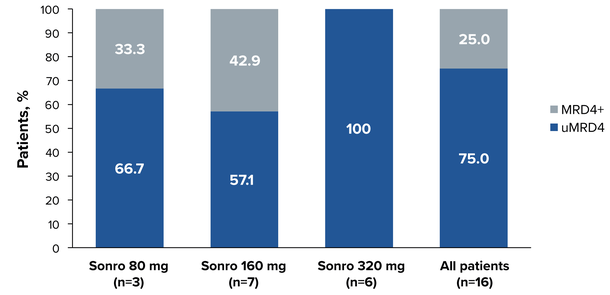
Abbreviations: CR, complete response; CRi, complete response with incomplete marrow recovery; ORR, overall response rate; PR, partial response; SD, stable disease; sonro, sonrotoclax.

Figure 4. Investigator-Assessed Responses



Abbreviations: BTK, Bruton tyrosine kinase; cBTKi, covalent BTK inhibitor; CR, complete response; CRi, complete response with incomplete marrow recovery; ncBTKi, noncovalent BTKi; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 5. Best Overall MRD in Peripheral Blood by Dose Level[a,b]



[a]Measured by ERIC-approved flow cytometry method with 10^{-4} sensitivity. uMRD4 defined as $<10^{-4}$ CLL cells of total WBCs. [b]Two patients were excluded from the MRD evaluable set: 1 patient in the 80-mg cohort had <200,000 total nucleated cells and 1 patient in the 320-mg cohort was missing all MRD samples.
Abbreviations: MRD, measurable residual disease; sonro, sonrotoclax; uMRD, undetectable MRD; WBC, white blood cell.

REFERENCES

1. Hillmen P, et al. *J Clin Oncol.* 2019;37(30):2722-2729.
2. Guo Y, et al. *J Med Chem.* 2024;67(10):7836-7858.
3. Hallek M, et al. *Blood.* 2018;131(25):2745-2760.

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DISCLOSURES

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