Frontline Treatment of Sonrotoclax (BGB-11417) + Zanubrutinib for CLL/SLL Demonstrates High uMRD Rates With Favorable Tolerability: Updated Data From BGB-11417-101, An Ongoing Phase 1/1b Study

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CONCLUSIONS

- Sonrotoclax in combination with zanubrutinib was generally safe and well tolerated, with a median relative dose intensity of 99% across all dose levels
  - No cases of laboratory or clinical tumor lysis syndrome occurred
  - Majority of TEAEs were low grade; low rates of transient gastrointestinal TEAEs, predominantly grade 1, were observed
  - The most common grade ≥3 TEAE was neutropenia, which was transient and did not lead to higher rates of grade ≥3 infections
  - 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
  - Sonrotoclax + zanubrutinib demonstrated a high response rate, including 100% ORR across all dose levels
  - With median follow-up of 30.7 months, no PFS events have been observed at the sonrotoclax RP2D of 320 mg
  - High blood uMRD4 rates were achieved early, with a median time to uMRD of 7.2 months, that continued to deepen over time with a best uMRD rate of 98% at data cutoff in the 320-mg cohort
  - No patient has progressed from uMRD4 to MRD4+ across both dose cohorts at data cutoff
- Sonrotoclax 320 mg in combination with zanubrutinib is currently being evaluated in patients with TN CLL in the phase 3 study, CELESTIAL-TNCLL (NCT06073821)

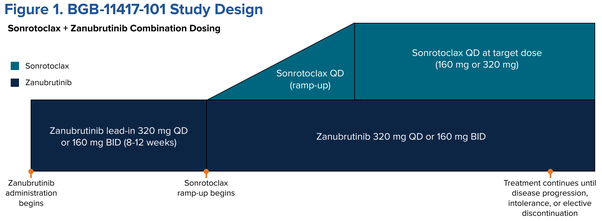
INTRODUCTION

- Frontline treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) with a B-cell lymphoma 2 (BCL2) inhibitor and a Bruton tyrosine kinase (BTK) inhibitor has emerged as an important treatment option that can induce high rates of undetectable minimal residual disease (uMRD)[1]
- A next-generation BCL2 inhibitor + BTK inhibitor combination is desired to improve the safety and efficacy of this treatment
- 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 progression-free survival (PFS) and favorable safety/tolerability compared with ibrutinib, including fewer cardiac adverse events (AEs), in patients with R/R CLL/SLL[6]
- Here, we report updated 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 (**Figure 1**)
- The study endpoints included safety and tolerability, recommended phase 2 dose, and overall response rate (ORR), defined as a partial response with lymphocytosis (PR-L) or better, and rate of MRD negativity as measured by ERIC-approved flow cytometry assay
- Treatment consisted of 8-12 weeks of zanubrutinib lead-in (320 mg once daily or 160 mg twice daily), then zanubrutinib + sonrotoclax until disease progression, intolerance, or elective discontinuation
- Patients who reach 96 weeks of combination treatment may elect to stop study drug treatment while remaining on study and entering long-term follow-up (protocol-defined elective discontinuation)

Figure 1. BGB-11417-101 Study Design

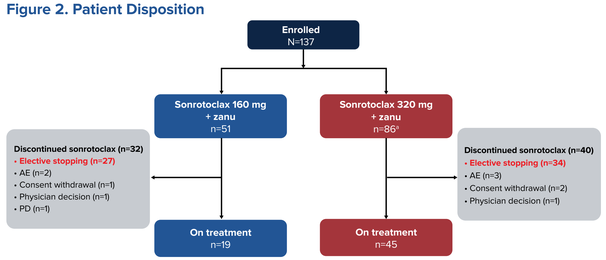


Abbreviations: BID, twice daily; C, cycle; D, day; QD, once daily.

RESULTS

- As of August 29, 2025, a total of 137 patients were enrolled in the sonrotoclax 160-mg (n=51) and 320-mg (n=86) cohorts (**Figure 2**)
  - At the data cutoff date, 47% of patients (n=64) remained on treatment
  - Most sonrotoclax discontinuations (85%; 61/72) were protocol-defined elective discontinuations after 96 weeks of sonrotoclax target dose
- Median study follow-up across cohorts was 30.7 months (range, 3.1-45.5 months)

Figure 2. Patient Disposition



Data cutoff: August 29, 2025.
[a]One patient received zanubrutinib but had not received sonrotoclax treatment.
Abbreviations: AE, adverse event; PD, progressive disease; zanu, zanubrutinib.

- Overall, median age was 62 years and 72% of patients were male (**Table 1**)
- At baseline, 29% (39/133) of tested patients had high tumor burden, 61% (82/135) had unmutated IGHV, and 14% (18/130) had *TP53* mutation or del(17p)

Table 1. 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	30.7 (17.5-45.5)	30.9 (3.1-41.9)	30.7 (3.1-45.5)
Age, median (range), years	63 (38-82)	61 (32-84)	62 (32-84)
≥65 years, n (%)	20 (39)	35 (41)	55 (40)
Male, n (%)	37 (73)	61 (71)	98 (72)
Disease type, n (%)			
CLL	48 (94)	82 (95)	130 (95)
SLL	3 (6)	4 (5)	7 (5)
Risk status, n/tested (%)			
del(17p)	6/46 (13)	8/83 (10)	14/129 (11)
TP53 mutation[a]	7/51 (14)	7/85 (8)	14/136 (10)
del(11q)	10/46 (22)	11/83 (13)	21/129 (16)
Unmutated IGHV, n/tested (%)	34/50 (68)	48/85 (56)	82/135 (61)
High tumor burden at baseline, n/tested (%)[b]	22/51 (43)	17/82 (21)	39/133 (29)

Data cutoff: August 29, 2025.
[a]*TP53* mutations defined as >10% VAF. [b]LNs ≥10 cm or LNs >5 cm and ALC >25×10⁹/L.
Abbreviations: ALC, absolute lymphocyte count; CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain variable region; LN, lymph node; SLL, small lymphocytic lymphoma; sonro, sonrotoclax; VAF, variant allele frequency; zanu, zanubrutinib.

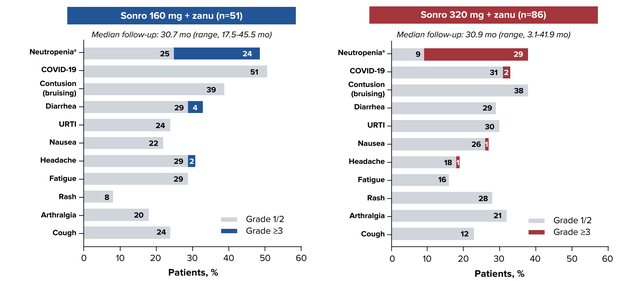
- The majority of treatment-emergent adverse events (TEAEs) occured at grades 1 and 2, and no TEAE led to death (**Table 2**)
  - The most common any-grade TEAEs were neutropenia (42%), COVID-19 (39%), contusion/bruising (39%), and diarrhea (31%) (**Figure 3**)
  - The most common grade ≥3 TEAE was neutropenia (27%), which was transient and did not lead to higher rates of grade ≥3 infections
- Five patients (4%) discontinued sonrotoclax treatment due to TEAEs
- No clinical or laboratory tumor lysis syndrome occurred
- Rates of diarrhea were similar across dose cohorts, with no grade ≥3 events in the 320-mg cohort

Table 2. Overall Safety Summary

Patients, n (%)	Sonro 160 mg + zanu (n=51)	Sonro 320 mg + zanu (n=86)[a]	All patients (N=137)
Any TEAEs	51 (100)	85 (99)	136 (99)
Grade ≥3	35 (69)	49 (57)	84 (61)
Serious TEAEs	19 (37)	26 (30)	45 (33)
Leading to death	0	0	0
Leading to discontinuation of zanu	2 (4)	6 (7)	8 (6)
Treated with sonro	51 (100)	85 (99)	136 (99)
Leading to discontinuation of sonro	2 (4)	3 (3)	5 (4)
Relative dose intensity of sonro, median, %	99	99	99
Duration of exposure, median (range), months	28.3 (5.8-45.5)	26.0 (0.8-41.9)	26.5 (0.8-45.5)

[a]One patient received zanubrutinib but had not received sonrotoclax treatment.
Abbreviations: sonro, sonrotoclax; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.

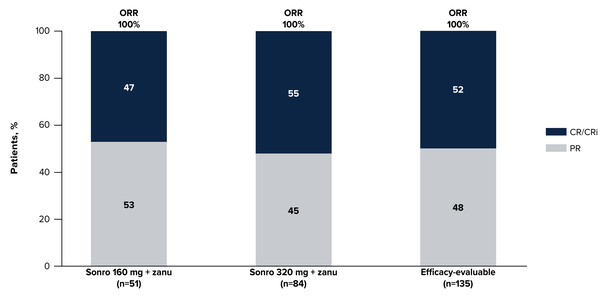
Figure 3. TEAEs in ≥15% of Patients



[a]Includes the combined preferred terms *neutrophil count decreased* and *neutropenia*.
Abbreviations: mo, month; sonro, sonrotoclax; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; zanu, zanubrutinib.

- In 135 efficacy-evaluable patients, ORR was 100%, with complete response (CR)/CR with incomplete marrow recovery (CRi) in 47% and 55% of the 160- and 320-mg cohorts, respectively (**Figure 4**)
  - Median time to first response was 2.6 months (range, 1.5-10.8 months)

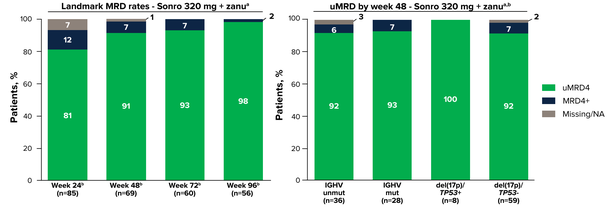
Figure 4. Overall Response Rates



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

- At data cutoff, the uMRD4 rates for 160-mg and 320-mg cohorts at 48 weeks of combination treatment were 84% and 91%, respectively
- uMRD4 rates continue to increase over time with 98% (55/56) of patients in the 320-mg cohort achieving uMRD4 by 96 weeks
- High rates of uMRD4 were achieved regardless of risk factors; no patient with uMRD4 reverted to MRD4+ (**Figure 5**)

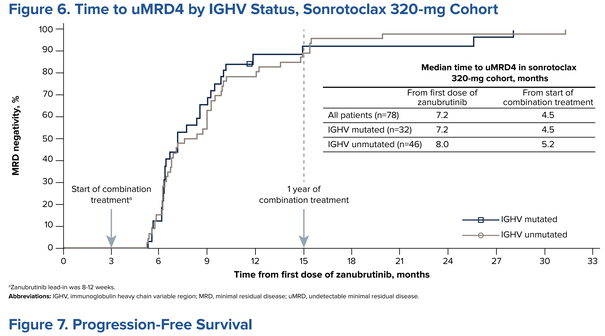
Figure 5. Landmark MRD Rates



[a]As measured by ERIC flow cytometry panel; uMRD4 = <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.
Abbreviations: IGHV, immunoglobulin heavy chain variable region; MRD, minimal residual disease; mut, mutated; NA, not assessable; sonro, sonrotoclax; uMRD, undetectable MRD; unmut, unmutated; zanu, zanubrutinib.

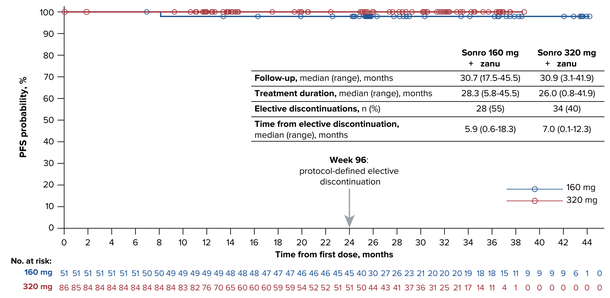
- Time to uMRD4 was similar, regardless of IGHV mutation status (**Figure 6**)
  - Median time from first zanubrutinib dose to uMRD4 was 7.2 months in the 320-mg cohort
  - Median time from start of combination treatment to uMRD4 was 4.5 months in the 320-mg cohort
- In the 320-mg cohort, 34 patients (40%) electively discontinued treatment after at least 96 weeks of therapy
  - Median time off treatment was 7.0 months (range, 0.1-12.3 months)
- With a median study follow up of 30.9 months, no progression was observed in the 320-mg cohort, including in those who have electively discontinued treatment (**Figure 7**)

Figure 6. Time to uMRD4 by IGHV Status, Sonrotoclax 320-mg Cohort



[a]Zanubrutinib lead-in was 8-12 weeks.
Abbreviations: IGHV, immunoglobulin heavy chain variable region; MRD, minimal residual disease; uMRD, undetectable minimal residual disease.

Figure 7. Progression-Free Survival



Abbreviations: PFS, progression-free survival; sonro, sonrotoclax; zanu, zanubrutinib.

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