P-06

Combination Treatment With Sonrotoclax (BGB-11417), a Second-Generation BCL2 Inhibitor, and Zanubrutinib, a BTK Inhibitor, is Well Tolerated and Achieves Deep Responses in Patients With Treatment-Naive CLL/SLL: Data From an Ongoing Phase 1/2 Study

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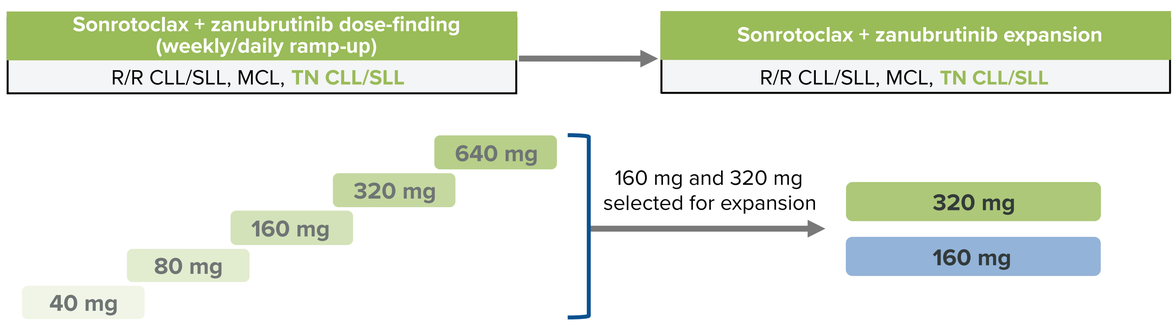
INTRODUCTION

- Sonrotoclax is a BH3 mimetic that binds and inhibits BCL2
  - >10-fold potency compared to ventoclax[1] and better in vitro activity against BCL2 mutations, including BCL2 G101V
  - Demonstrated high selectivity
  - Short half-life (4 hours)
- The combination of BCL2 and Bruton tyrosine kinase (BTK) inhibitors has shown synergistic activity in preclinical chronic lymphocytic leukemia (CLL) models[2-5]
- Ibrutinib with venetoclax in patients with CLL/small lymphocytic lymphoma (SLL) is effective, however, toxicities can limit use[6]
- Zanubrutinib is highly effective in patients with treatment naive (TN) and relapsed/refractory (R/R) CLL including those with high-risk diseases,[7,8] demonstrating a superior efficacy and safety profile, including less cardiovascular toxicity than ibrutinib in R/R CLL[8]
- Here, we report preliminary results of the BGB-11417-101 trial (NCT04277637) in patients with TN CLL/SLL treated with sonrotoclax in combination with zanubrutinib

METHODS

- BGB-11417-101 is a phase 1/2 study evaluating sonrotoclax as monotherapy, in combination with zanubrutinib, and in combination with obinutuzumab ± zanubrutinib in patients with B-cell malignancies (**Figure 1**)
- Main study objectives (TN CLL cohorts): determine safety and tolerability and define the RP2D of sonrotoclax when given in combination with zanubrutinib (160 mg BID or 320 mg QD)
- 8 to 12 weeks of zanubrutinib monotherapy was given prior to sonrotoclax dosing (12 weeks if high tumor burden)
- Sonrotoclax was dosed orally, once daily, using a weekly or daily ramp-up schedule to reach the target dose

Figure 1. BGB-11417-101 Study Design



RESULTS

Table 1. Baseline Characteristics

Characteristics	Sonrotoclax 160 mg + zanu (n=51)	Sonrotoclax 320 mg + zanu (n=56)	All Patients (N=107)
Study follow up time, median (range), months	7.2 (0.3-21.1)	9.8 (0.5-17.4)	9.7 (0.3-21.1)
Age, median (range), years	63 (38-82)	61 (34-84)	62 (34-84)
≥65 years, n (%)	20 (39)	19 (34)	39 (36)
≥75 years, n (%)	4 (8)	7 (13)	11 (10)
Sex, n (%)			
Male	37 (73)	44 (79)	81 (76)
Disease type, n (%)			
CLL	49 (96)	52 (93)	101 (94)
SLL	2 (4)	4 (7)	6 (6)
Risk status, n/tested (%)[a]			
del(17p)	6/49 (12)	6/54 (11)	12/103 (12)
del(17p) and/or *TP53*^{mut}	12/50 (24)	15/55 (27)	27/105 (26)
IGHV status, n/tested (%)			
Unmutated	33/47 (70)	28/51 (55)	61/98 (62)
Tumor bulk at baseline, n (%)			
High[b]	20 (39)	14 (25)	34 (32)
Not High	31 (61)	42 (75)	73 (68)

Data cutoff: August 15, 2023.
[a] *TP53* mutations defined as >10% VAF. [b] Nodes ≥10 cm or nodes >5 cm and ALC >25×10^9/L.
ALC, absolute lymphocyte count.

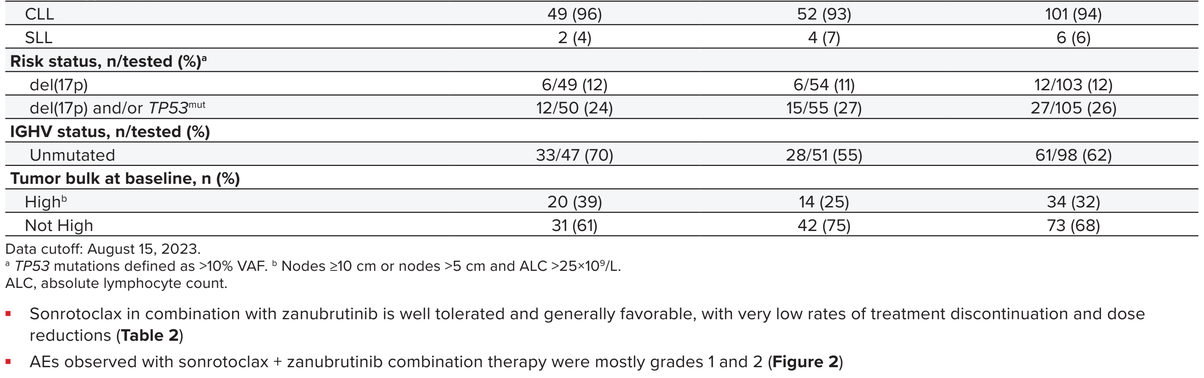
- Sonrotoclax in combination with zanubrutinib is well tolerated and generally favorable, with very low rates of treatment discontinuation and dose reductions (**Table 2**)
- AEs observed with sonrotoclax + zanubrutinib combination therapy were mostly grades 1 and 2 (**Figure 2**)

Table 2. Dose Modification and AE Summary

	Sonrotoclax 160 mg + zanu (n=51)	Sonrotoclax 320 mg + zanu (n=56)	All Patients (N=107)
Any AEs, n (%)	47 (92.2)	49 (87.5)	96 (89.7)
Grade ≥3	22 (43.1)	21 (37.5)	43 (40.2)
Serious AEs	7 (13.7)	8 (14.3)	15 (14.0)
Leading to death	0	0	0
Leading to dose reduction of zanubrutinib	1 (2.0)	2 (3.6)	3 (2.8)
Leading to discontinuation of zanubrutinib[a]	1 (2.0)	0	1 (0.9)
Treated with sonrotoclax, n (%)	41 (80.4)	53 (94.6)	94 (87.9)
Leading to hold of sonrotoclax	11 (26.8)	10 (18.9)	21 (22.3)
Leading to dose reduction of sonrotoclax	2 (4.9)	3 (5.7)	5 (5.3)
Leading to discontinuation of sonrotoclax[a]	1 (2.4)	0	1 (1.1)

[a] One patient stopped both sonrotoclax and zanubrutinib due to fungal infection.

Figure 2. Most Frequent AEs (Incidence ≥5 Patients)[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.
GERD, gastroesophageal reflux disease; Gr, grade; URTI, upper respiratory tract infection.

Table 3. TEAEs of Interest

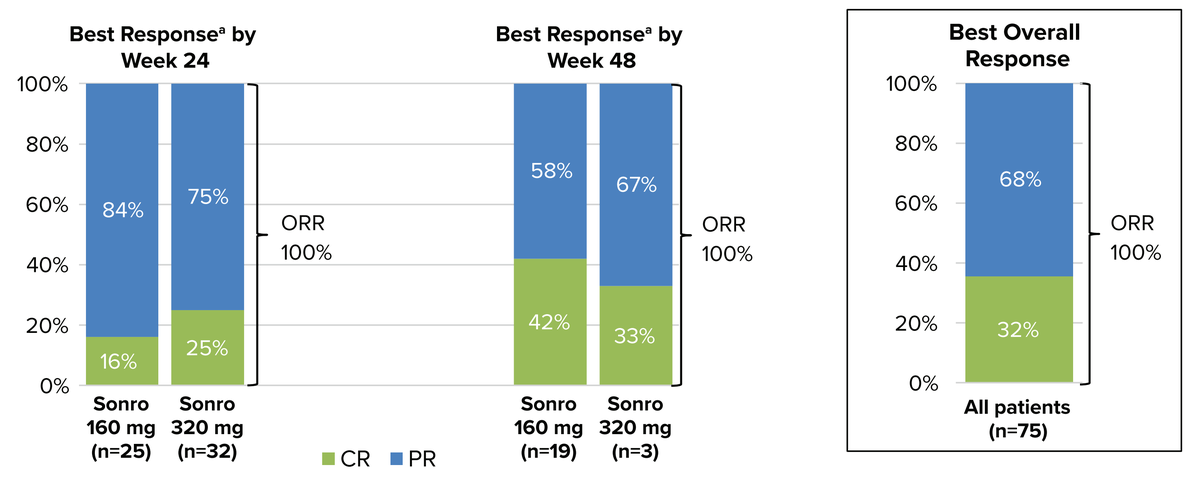
TLS[a]	No clinical or laboratory TLS was observed with weekly or daily ramp-up
GI toxicity[b]	Diarrhea events were mostly grade 1; no dose reductions occurred
Atrial fibrillation	No atrial fibrillation was observed
Neutropenia	Most frequent AE (and grade ≥3 AE); 1 dose reduction/no dose holds, 18 patients (17%) used G-CSF[c]
Febrile neutropenia	Observed in 2 patients (2%) assigned to the 160 mg dose level; events resolved without sequelae
Infections	Low rate of grade ≥3 infections (8%); pneumonia (n=4) was the only grade ≥3 infection in more than 1 patient

[a] TLS, tumor lysis syndrome, defined by Howard criteria. [b] One patient experienced multiple episodes of grade 2 diarrhea so ramp-up was paused at 80 mg, they subsequently increased to 160 mg. [c] Includes all patients reporting G-CSF use during treatment, regardless of whether it was used for neutropenia or prophylaxis. G-CSF was used in 7 patients in the 160 mg cohort (14%) and 11 patients in the 320 mg cohort (20%). The median duration was 10 days.
G-CSF, granulocyte-colony stimulating factor.

CONCLUSIONS

- Sonrotoclax 160 or 320 mg in combination with zanubrutinib 320 mg QD was safe and well tolerated
  - No tumor lysis syndrome, no cardiac toxicity, and low rates of gastrointestinal AEs (predominantly grade 1) occurred
- Efficacy was very promising in this all-comer TN CLL population
  - ORR was 100%
  - High rate of blood MRD negativity occurred by Week 24, with deepening response by Week 48 of combination therapy
  - No PFS events were observed as of the data cut off
  - 106/107 of patients remain on treatment
- Based on these data, sonrotoclax 320 mg was selected for the phase 3 study with zanubrutinib in TN CLL

Figure 3. Overall Response Rate

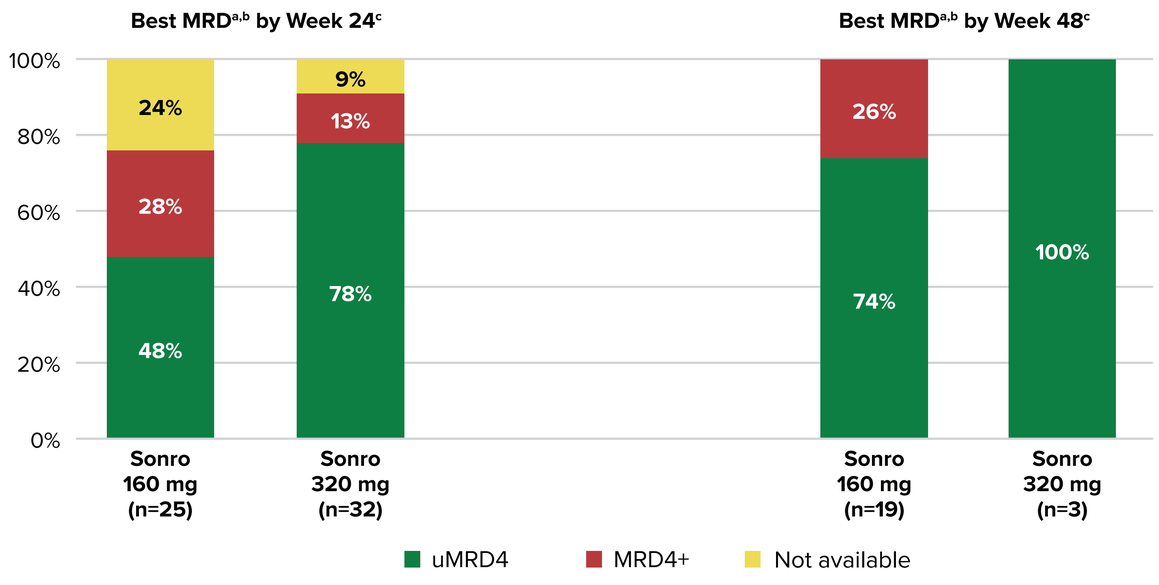


Response rates improved with time

[a] Percentage of response is based on number of patients who have reached the assessment at 24 or 48 weeks after completion of ramp-up, following zanubrutinib monotherapy and sonrotoclax ramp-up to target dose.

- A high rate of undetectable minimal residual disease (uMRD) was achieved at both 160 mg and 320 mg with evidence of deepening response over time (**Figure 4**)
  - A trend for higher uMRD rates was observed with 320 mg
  - Evidence of deepening response over time
- At a median follow-up of 9.7 months, no patient has experienced disease progression or died at either sonrotoclax dose level (**Figure 5**)

Figure 4. Minimal Residual Disease in Peripheral Blood



[a] MRD was measured by ERIC flow cytometry with 10^{-4} sensitivity. uMRD4 is defined as the number of CLL cells of total nucleated cells <10^{-4}. MRD4+ is defined as the number of CLL cells of total nucleated cells >10^{-4}; [b] MRD is best reported within a 2-week window following the Week 24 Day 1 and Week 48 Day 1 MRD assessment timepoints, respectively;
[c] Week 24 or 48 represents 24 or 48 weeks at target dose, following zanubrutinib monotherapy and sonrotoclax ramp-up to target dose.

Figure 5. Progression-Free Survival

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DISCLOSURES

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