Combination Treatment With Novel B-Cell Lymphoma 2 Inhibitor Sonrotoclax (BGB-11417) and Zanubrutinib in Patients With Relapsed/Refractory Mantle Cell Lymphoma: Results From a Phase 1/1b Study

PF933

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CONCLUSIONS

- Sonrotoclax + zanubrutinib, an emerging combination therapy for B-cell malignancies, demonstrated a favorable safety profile as well as deep and durable responses in patients with R/R MCL
  - No laboratory or clinical TLS occurred
  - The majority of TEAEs were low grade, and no new safety signals were identified
  - In the sonrotoclax 320-mg/RP2D cohort, the ORR was 81.5%, the CR rate was 59.3%, and the estimated 24-month DOR rate was 78.3%
- Sonrotoclax + zanubrutinib combination therapy is currently being evaluated for R/R MCL in the phase 3 registrational study, CELESTIAL-RRMCL (NCT06742996)

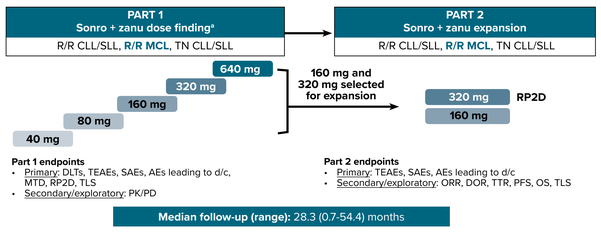
INTRODUCTION

- Mantle cell lymphoma (MCL) is a rare and currently incurable subtype of B-cell non-Hodgkin lymphoma, characterized by continuous relapses after short periods of remission[1]
  - In a recent phase 3 study, combination therapy with a B-cell lymphoma 2 (BCL2) inhibitor + Bruton tyrosine kinase (BTK) inhibitor improved progression-free survival (PFS) in patients with relapsed/refractory (R/R) MCL compared with ibrutinib monotherapy[2]
  - However, this combination regimen is not approved for patients with MCL, and novel treatments with improved tolerability are needed
- 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[3,4]
  - In May 2026, sonrotoclax received accelerated approval from the US FDA for patients with R/R MCL who had previously received ≥2 lines of therapy, including a BTK inhibitor[5]
- Zanubrutinib, a highly selective and potent next-generation covalent BTK inhibitor approved for patients with R/R MCL, was designed to provide complete and sustained BTK occupancy for efficacy across multiple B-cell malignancies, with fewer off-target adverse events (AEs) compared with other BTK inhibitors[6,7]
- Here, updated safety and efficacy data are reported from a phase 1/1b study of sonrotoclax + zanubrutinib combination therapy in patients with R/R MCL

METHODS

- BGB-11417-101 (NCT04277637) is an ongoing, global, dose selection and expansion study evaluating sonrotoclax as monotherapy or in combination with zanubrutinib in patients with mature B-cell malignancies (**Figure 1**)
- For the MCL cohort, eligible patients had R/R disease and received ≥1 prior systemic therapy
- Zanubrutinib monotherapy (320 mg once daily [QD] or 160 mg twice daily) was administered for 8-12 weeks, followed by sonrotoclax + zanubrutinib until disease progression, unacceptable toxicity, or protocol-defined elective discontinuation after week 96
- Sonrotoclax target doses (80, 160, 320, or 640 mg QD) were achieved through gradual dose ramp-up over approximately 4 weeks to mitigate the risk of tumor lysis syndrome (TLS)

Figure 1. BGB-11417-101 Study Design



[a]The safety monitoring committee reviewed dose-level cohort data before dose escalation.
Abbreviations: AE, adverse event; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; d/c, discontinuation; DLT, dose-limiting toxicity; DOR, duration of response; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; SAE, serious adverse event; sonro, sonrotoclax; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; TN, treatment naive; TTR, time to response; zanu, zanubrutinib.

RESULTS

- As of March 1, 2026, a total of 51 patients with R/R MCL were enrolled, including 27 in the sonrotoclax 320-mg cohort, which was the selected recommended phase 2 dose (RP2D) (**Table 1**)
- At the data cutoff, 46 of 51 patients (90.2%) started sonrotoclax + zanubrutinib (5 patients had disease progression during zanubrutinib lead-in) and 22 (43.1%) remained on treatment
  - Twenty-four patients (47.1%) discontinued sonrotoclax, most commonly due to disease progression (n=11) and elective discontinuation (n=7)

Table 1. Baseline Characteristics

	Sonro 320 mg/ RP2D + zanu (n=27)	All (N=51)
Study follow-up, median (range), mo	28.3 (0.7-54.4)	
Age, median (range), y	67.0 (45-85)	68.0 (45-85)
Male, n (%)	17 (63.0)	36 (70.6)
ECOG PS, n (%)		
0	6 (22.2)	21 (41.2)
1	20 (74.1)	29 (56.9)
2	1 (3.7)	1 (2.0)
High tumor bulk, n (%)[a]	3 (11.1)	6 (11.8)
Ki-67 proliferation index, n (%)		
<30%	11 (40.7)	18 (35.3)
≥30%	4 (14.8)	10 (19.6)
Missing	12 (44.4)	23 (45.1)
***TP53* mutation status, n (%)**		
Mutated	12 (44.4)	21 (41.2)
Unmutated	14 (51.9)	28 (54.9)
Missing	1 (3.7)	2 (3.9)
No. of prior lines of therapy, median (range)	1 (1-3)	1 (1-4)
No. of prior lines of therapy, n (%)		
1	20 (74.1)	41 (80.4)
2	3 (11.1)	5 (9.8)
≥3	4 (14.8)	5 (9.8)
Prior BTK inhibitor treatment, n (%)[b]	4 (14.8)	4 (7.8)
Duration, median (range), mo	7.1 (0.3-25.0)	7.1 (0.3-25.0)
Prior SCT, n (%)		
Allogeneic	1 (3.7)	1 (2.0)
Autologous	7 (25.9)	14 (27.5)
Prior CAR-T therapy, n (%)	1 (3.7)	1 (2.0)

Data cutoff: March 1, 2026.
[a]Any lymph node ≥10 cm or lymph node ≥5 cm and ALC ≥25×10[9]/L. [b]All patients discontinued prior BTK inhibitor treatment for reasons other than PD.
Abbreviations: ALC, absolute lymphocyte count; BTK, Bruton tyrosine kinase; CAR-T, chimeric antigen receptor T-cell; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; PD, progressive disease; SCT, stem cell transplant; sonro, sonrotoclax; zanu, zanubrutinib.

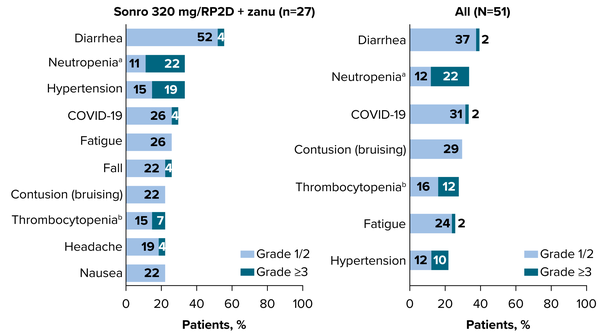
- Across all cohorts, the most common any-grade treatment-emergent AEs were diarrhea (39.2%), neutropenia (33.3%), and COVID-19 (33.3%) (**Figure 2**)
  - In the sonrotoclax 320-mg/RP2D cohort, the most common any-grade AE was diarrhea (55.6%; grade ≥3, 3.7%)
- Grade ≥3 AEs occurred in 64.7% of patients (**Table 2**); neutropenia (21.6%) was the most common
  - The most common grade ≥3 AE seen with sonrotoclax 320 mg/RP2D was neutropenia (22.2%)
  - One grade 3 AE of atrial fibrillation was observed in a patient in the sonrotoclax 320-mg/RP2D cohort who had a prior history of atrial fibrillation
- Serious AEs occurred in 41.2% of all patients; pneumonia (15.7%) was the most common
- AEs led to discontinuation of sonrotoclax + zanubrutinib in five patients (9.8%) and zanubrutinib alone in three (5.9%); none led to discontinuation of sonrotoclax only
- AEs led to death in four patients (7.8%): pneumonia (sonrotoclax 160 mg; related to sonrotoclax and zanubrutinib), pleural effusion due to progressive disease (PD) (sonrotoclax 80 mg; unrelated to study drug), abdominal sepsis (sonrotoclax 320 mg/RP2D; unrelated to study drug), and encephalopathy (sonrotoclax 640 mg; unrelated to study drug)
- No laboratory or clinical TLS occurred

Table 2. Safety Summary

Patients, n (%)	Sonro 320 mg/ RP2D + zanu (n=27)	All (N=51)
Any treatment-emergent AE	26 (96.3)	49 (96.1)
Grade ≥3	18 (66.7)	33 (64.7)
Serious	11 (40.7)	21 (41.2)
Leading to death	1 (3.7)	4 (7.8)[a]
Leading to zanu discontinuation	4 (14.8)	8 (15.7)[b,c]
Treated with sonro	24 (88.9)	46 (90.2)
Leading to sonro discontinuation	2 (7.4)	5 (9.8)[c]
Duration of exposure to study drugs, median (range), mo	18.3 (0.7-42.9)	24.3 (0.7-54.4)

[a]Due to pleural effusion (80 mg; due to PD), abdominal sepsis (320 mg), pneumonia (160 mg), and encephalopathy (640 mg). [b]Includes three patients who discontinued zanubrutinib only due to diarrhea (80 mg), abdominal pain (320 mg), and cryptococcal meningoencephalitis (320 mg). [c]Includes patients who discontinued sonrotoclax and zanubrutinib due to lymph node pain (160 mg; due to PD), pneumonia (160 mg; due to PD), diarrhea (320 mg), myelodysplastic syndrome (160 mg), and abdominal sepsis (320 mg).
Abbreviations: AE, adverse event; PD, progressive disease; RP2D, recommended phase 2 dose; sonro, sonrotoclax; zanu, zanubrutinib.

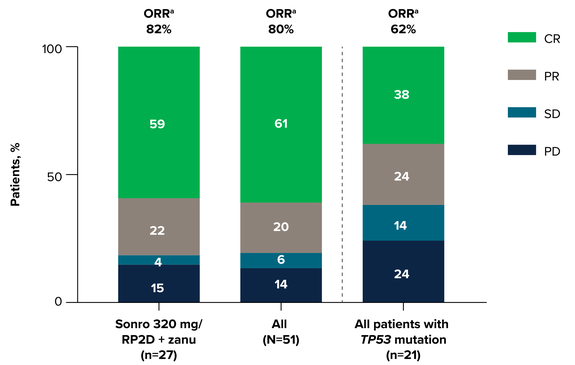
Figure 2. Treatment-Emergent AEs in ≥20% of Patients



[a]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
Abbreviations: AE, adverse event; sonro, sonrotoclax; zanu, zanubrutinib.

- In evaluable patients (N=51), the overall response rate (ORR) was 80.4%, with a complete response (CR) rate of 60.8% (**Figure 3**)
- In the sonrotoclax 320-mg/RP2D cohort, ORR was 81.5% and CR rate was 59.3%
  - Median time to CR was 5.2 mo (range, 1.5-32.5 mo)
  - Of 16 patients who achieved CR, 87.5% (n=14) remain in CR
  - The duration of CR rate at 24 mo was 86.5% (95% CI, 55.8%-96.5%)
  - Of four evaluable BTK inhibitor-pretreated patients, two achieved partial response
- All patients with a best overall response of PD (n=7) had progression during zanubrutinib lead-in, including four patients in the sonrotoclax 320-mg/RP2D cohort
- Seven patients (sonrotoclax 80 mg, n=1; 160 mg, n=3; 320 mg/RP2D, n=3) electively discontinued treatment after ≥96 weeks of combination therapy, with a median time off treatment of 12.0 mo (range, 0.6-14.9 mo); as of the data cutoff date, six patients (85.7%) remain progression-free

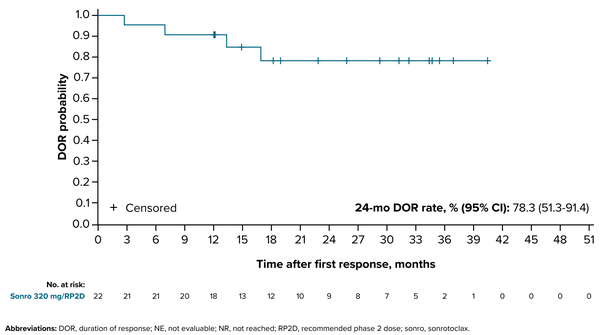
Figure 3. Overall Response Rates



[a]ORR was defined as PR or better per Lugano 2014 criteria.
Abbreviations: CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease; sonro, sonrotoclax; zanu, zanubrutinib.

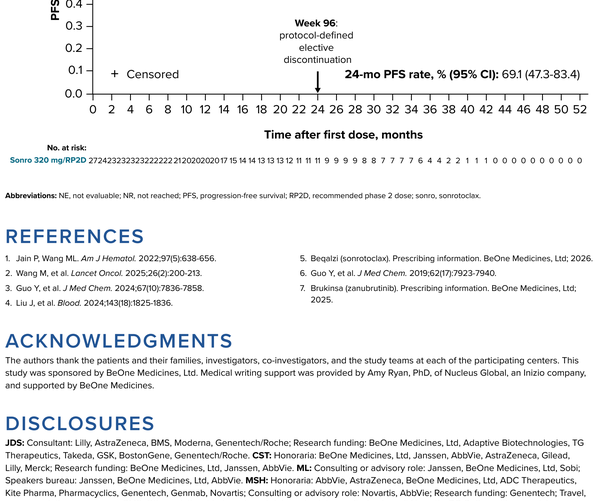
- With a median study follow-up of 28.3 mo (range, 0.7-54.4 mo), the median duration of response (DOR) was 50.9 mo (95% CI, 34.8-not evaluable [NE]) across all cohorts
  - In the sonrotoclax 320-mg/RP2D cohort, median DOR was not reached (**Figure 4**); the 24-mo DOR rate was 78.3% (95% CI, 51.3%-91.4%; median DOR follow-up, 25.8 mo)
- Across all patients, median PFS was 52.5 mo (95% CI, 24.7-NE)
  - In the sonrotoclax 320-mg/RP2D cohort, median PFS was not reached (**Figure 5**); the 24-mo PFS rate was 69.1% (95% CI, 47.3%-83.4%; median study follow-up, 24.1 mo)

Figure 4. Duration of Response: Sonrotoclax 320-mg/RP2D Cohort



Abbreviations: DOR, duration of response; NE, not evaluable; NR, not reached; RP2D, recommended phase 2 dose; sonro, sonrotoclax.

Figure 5. Progression-Free Survival: Sonrotoclax 320-mg/RP2D Cohort



Abbreviations: NE, not evaluable; NR, not reached; PFS, progression-free survival; RP2D, recommended phase 2 dose; sonro, sonrotoclax.

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