Combination Treatment With Novel BCL2 Inhibitor Sonrotoclax (BGB-11417) + Zanubrutinib Induces High Rate of Complete Remission for Patients With Relapsed/Refractory Mantle Cell Lymphoma

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Introduction

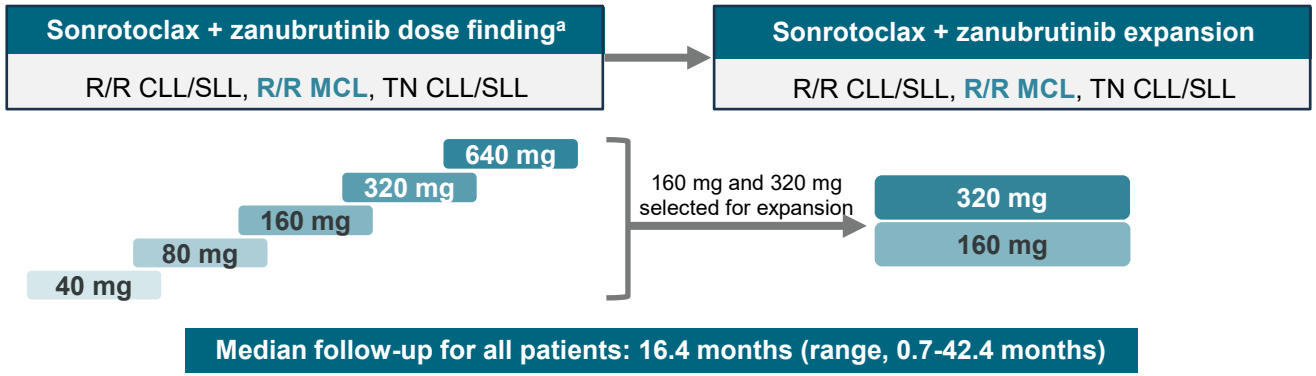
- MCL is an uncommon, incurable subtype of aggressive B-cell non-Hodgkin lymphoma[1]
- Venetoclax has demonstrated efficacy in patients with R/R MCL; however, it is not currently approved to treat R/R MCL[2]
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation[3,4]
- Zanubrutinib, a next-generation covalent BTK inhibitor, was designed to provide complete and sustained BTK occupancy for efficacy across multiple B-cell malignancies, with fewer off-target AEs compared with other BTK inhibitors, and is approved for R/R MCL[5,6]
- Here, updated safety and efficacy data for patients with R/R MCL treated with sonrotoclax + zanubrutinib in the ongoing BGB-11417-101 study are presented

AE, adverse event; BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; R/R, relapsed/refractory.

1. Jain P, Wang ML. *Am J Hematol.* 2022;97(5):638-656. 2. Wang M, et al. ASH 2023. Abstract LBA-2. 3. Guo Y, et al. *J Med Chem.* 2024;67(10):7836-7858. 4. Liu J, et al. *Blood.* 2024;143(18):603-608.
5. Guo Y, et al. *J Med Chem.* 2019;62(17):7923-7940. 6. Brukinsa. Prescribing information. BeiGene, Ltd; 2024.

BGB-11417-101 (NCT04277637) Study Design

- 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
  - Data from R/R MCL cohorts treated with sonrotoclax + zanubrutinib are the focus of this presentation
- The primary endpoints were safety per CTCAE v5.0, MTD, and RP2D
- For the R/R MCL cohorts, treatment consisted of 8-12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID), then zanubrutinib + sonrotoclax until disease progression, intolerance, or elective discontinuation
- Patients who reached 96 weeks of combination treatment could elect to stop study drug treatment while remaining on study and following all procedures (protocol-defined elective discontinuation)



[a]The safety monitoring committee reviewed dose-level cohort data before dose escalation.
BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; QD, once daily; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; TN, treatment naive.

Baseline Characteristics and Demographics

Characteristic	Sonro 80 mg + Zanu (n=6)	Sonro 160 mg + Zanu (n=13)	Sonro 320 mg + Zanu (n=27)	Sonro 640 mg + Zanu (n=5)	All (N=51)
Study follow-up, median (range), months	40.4 (3.9-42.4)	16.4 (1.0-38.5)	13.2 (0.7-31.6)	15.8 (3.4-21.5)	16.4 (0.7-42.4)
Age, median (range), years	60.0 (46-84)	69.0 (45-81)	67.0 (45-85)	71.0 (68-80)	68.0 (45-85)
Male, n (%)	5 (83.3)	11 (84.6)	17 (63.0)	3 (60.0)	36 (70.6)
ECOG PS, n (%)					
0	4 (66.7)	8 (61.5)	6 (22.2)	3 (60.0)	21 (41.2)
1	2 (33.3)	5 (38.5)	20 (74.1)	2 (40.0)	29 (56.9)
Tumor bulk,[a] n (%)					
High	1 (16.7)	2 (15.4)	4 (14.8)	0	7 (13.7)
Ki67 proliferation index, n (%)					
<30%	3 (50.0)	3 (23.1)	8 (29.6)	1 (20.0)	15 (29.4)
≥30%	2 (33.3)	2 (15.4)	4 (14.8)	2 (40.0)	10 (19.6)
Missing	1 (16.7)	8 (61.5)	15 (55.6)	2 (40.0)	26 (51.0)
***TP53* mutation status, n (%)**					
Mutated	2 (33.3)	1 (7.7)	1 (3.7)	2 (40.0)	6 (11.8)
Unmutated	0	3 (23.1)	3 (11.1)	1 (20.0)	7 (13.7)
Missing	4 (66.7)	9 (69.2)	23 (85.2)	2 (40.0)	38 (74.5)
Prior therapy					
No. of lines of prior therapy, median (range)	1 (1-1)	1 (1-4)	1 (1-3)	1 (1-1)	1 (1-4)
Prior BTK inhibitor, n (%)	0	0	4 (14.8)	0	4 (7.8)
Prior BTK inhibitor duration, median (range), months	NA	NA	8.4 (0.3-24.1)	NA	8.4 (0.3-24.1)

Data cutoff: March 1, 2025.

[a]High tumor bulk: any lymph node ≥10 cm or lymph node ≥5cm and ALC ≥25 × 10^9/L.

ALC, absolute lymphocyte count; BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not applicable; sonro, sonrotoclax; TLS, tumor lysis syndrome; zanu, zanubrutinib.

Sonrotoclax in Combination With Zanubrutinib is Well Tolerated Across All Dose Levels

- Safety profile was generally similar across all doses tested and sonrotoclax 160-mg and 320-mg doses were chosen for expansion
- No DLTs occurred and MTD was not reached up to sonrotoclax 640 mg; 320 mg was chosen as RP2D

Patients, n (%)	Sonro 80 mg + Zanu (n=6)	Sonro 160 mg + Zanu (n=13)	Sonro 320 mg + Zanu (n=27)	Sonro 640 mg + Zanu (n=5)	All (N=51)
Any TEAEs	4 (66.7)	13 (100)	26 (96.3)	5 (100)	48 (94.1)
Grade ≥3	4 (66.7)	7 (53.8)	14 (51.9)	3 (60.0)	28 (54.9)
Serious TEAEs	3 (50.0)	4 (30.8)	7 (25.9)	1 (20.0)	15 (29.4)
Leading to death	1 (16.7)	1 (7.7)	1 (3.7)	0	3 (5.9)[a]
Leading to zanu discontinuation	1 (16.7)	3 (23.1)	4 (14.8)	0	8 (15.7)[b]
Leading to zanu dose reduction	1 (16.7)	1 (7.7)	0	0	2 (3.9)
Treated with sonro	6 (100)	11 (84.6)	24 (88.9)	5 (100)	46 (90.2)
Leading to death	0	1 (7.7)	0	0	1 (2.0)[c]
Leading to sonro discontinuation	0	3 (23.1)	2 (7.4)	0	5 (9.8)[d]
Leading to sonro dose reduction	0	0	0	0	0

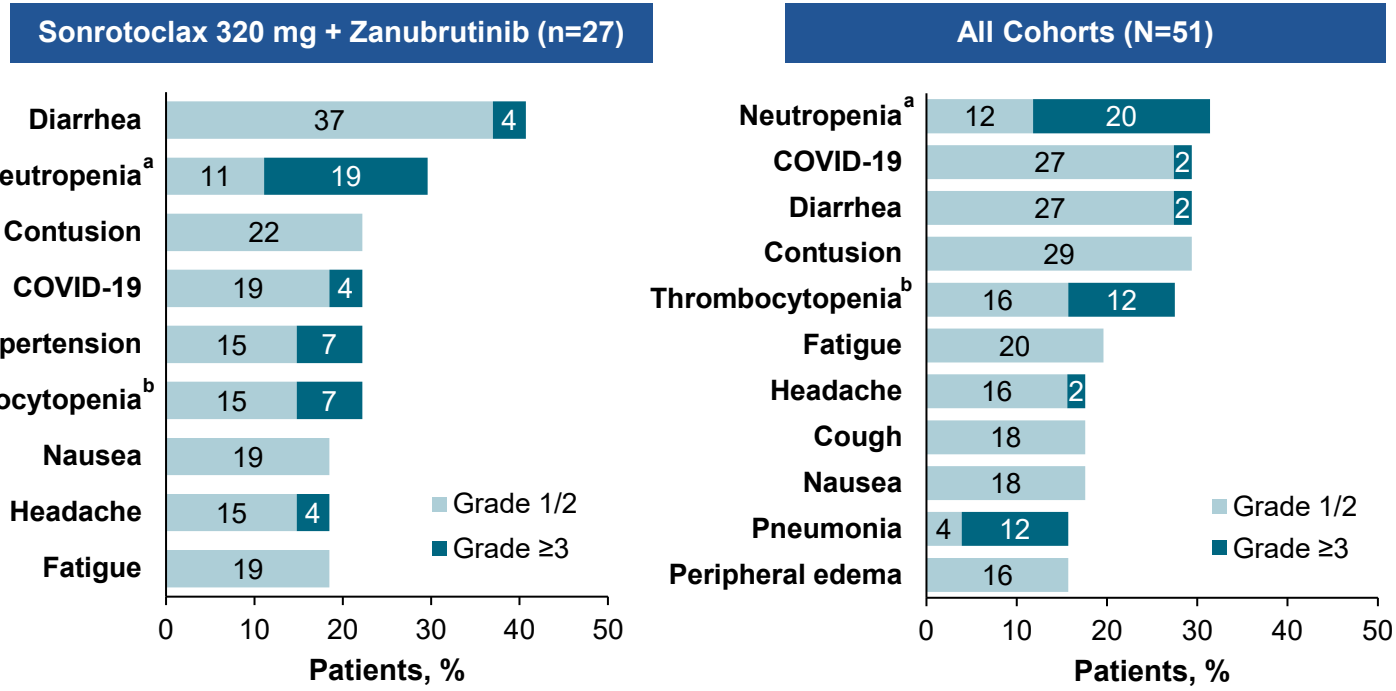
[a]Pleural effusion (160 mg; due to PD), abdominal sepsis (320 mg), pneumonia (160 mg). [b]Lymph node pain (160 mg, due to PD), diarrhea (320 mg), MDS (160 mg), abdominal sepsis (320 mg), pneumonia (160 mg), diarrhea (80 mg), cryptococcal meningoencephalitis (320 mg), abdominal pain (320 mg). [c]Pneumonia (160 mg). [d]Diarrhea (320 mg), MDS (160 mg), abdominal sepsis (320 mg), pneumonia (160 mg), lymph node pain (160 mg, due to PD).

DLT, dose-limiting toxicity; MDS, myelodysplastic syndrome; MTD, maximum tolerated dose; PD, progressive disease; RP2D, recommended phase 2 dose; sonro, sonrotoclax; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.

Most TEAEs Observed With Sonrotoclax + Zanubrutinib Were Low Grade and Transient

- No laboratory or clinical TLS
- No atrial fibrillation/flutter

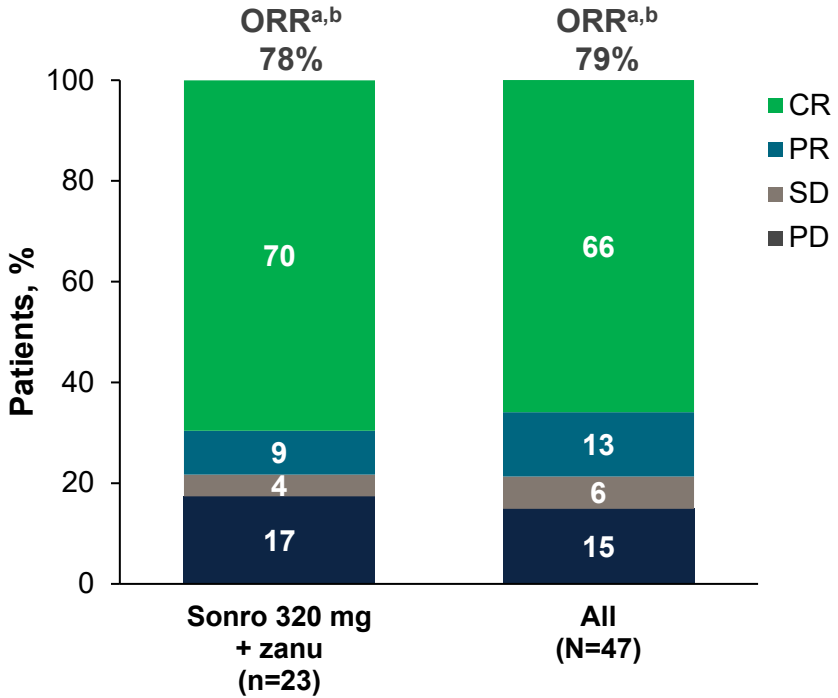
TEAEs in ≥15% of patients at the sonrotoclax RP2D (320 mg) and in all patients



[a]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome.

Sonrotoclax + Zanubrutinib Demonstrated Deep Responses Across All Dose Levels

- With a median study follow-up of 16.4 months, ORR[a,b] was 79% with a CR rate of 66% across all doses in efficacy-evaluable patients
  - ORR was 78% in the 320-mg dose group, with a CR rate of 70%
  - **All patients who had a BOR of PD progressed during zanubrutinib lead-in (4 patients in the 320-mg cohort)**
- The median time to CR was 6.7 months (range, 1.5-28.2 months)
- Of 4 evaluable patients with prior BTK inhibitor therapy, 1 achieved PR and 1 achieved CR

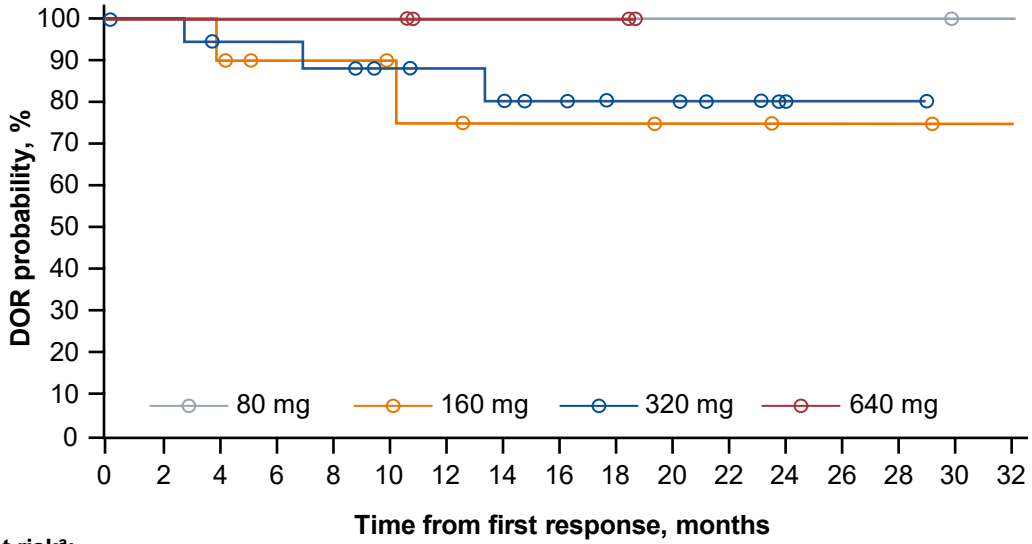


	Sonro 320 mg + zanu (n=23)	All (N=47)
Study follow-up,[c] median (range), months	13.2 (0.7-31.6)	16.4 (0.7-42.4)

[a]Responses were assessed per Lugano 2014 criteria and are shown as the percentages of responding patients who had ≥1 post-baseline tumor assessment after dosing with sonrotoclax unless treatment was discontinued due to clinical progression or death prior to tumor assessment. [b]ORR was defined as PR or better. [c]For all patients as treated (N=51).
BOR, best overall response; BTK, Bruton tyrosine kinase; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Sonrotoclax + Zanubrutinib Demonstrated Durable Responses

- Median DOR in all patients was not reached (95% CI, 34.8-NE)
  - DOR rate at 24 months was 84.0% (95% CI, 65.3%-93.1%; mFU, 17.7 months)
- Median DOR in the 320-mg dose group was not reached (95% CI, 3.3-NE)
  - DOR rate at 24 months was 80.1% (95% CI, 49.4%-93.3%; mFU, 14.8 months)
- Of 18 patients in the 320-mg dose group who achieved CR[a], 16 remain in CR (mFU, 13 months)
  - DoCR rate at 18 months was 84.4% (95% CI, 50.4%-95.9%; mFU, 10.2 months)



No. at risk[a]:

80 mg	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4	4	4			
160 mg	10	10	10	10	9	8	7	7	7	7	6	5	5	4	4	4	4	4	4	4	4	3	3	3	3	2	2	2	2	2	2	1	1	1		
320 mg	22	18	18	17	15	15	15	14	14	13	12	11	11	11	10	8	8	7	6	6	6	5	4	4	1	1	1	1	1	0	0	0	0			
640 mg	4	4	4	4	4	4	4	4	4	4	4	2	2	2	2	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0			

[a]For all patients as treated (N=51).
CR, complete response; DoCR, duration of complete response; DOR, duration of response; mFU, median follow-up; NE, not evaluable.

Sonrotoclax + Zanubrutinib Demonstrated Encouraging Safety and Antitumor Activity in Patients With R/R MCL

- Sonrotoclax + zanubrutinib combination treatment had a tolerable safety profile in patients with R/R MCL at all dose levels tested up to 640 mg; 320 mg was declared as the RP2D
  - No laboratory or clinical TLS occurred
  - Majority of TEAEs were low grade, and no new safety signals were identified across dose levels
  - No atrial fibrillation/flutter was observed
- Antitumor activity was promising, with high response rates and early, durable, and deep responses in patients with R/R MCL
  - Across all doses, ORR was 79% with a CR rate of 66%; at the RP2D of 320 mg, ORR was 78% with a CR rate of 70%
  - At a median DOR follow-up of 17.7 months (range, 10.7-23.1 months), the estimated event-free DOR rate at 24 months was 84% (95% CI, 65.3%-93.1%) across all dose levels
- Building on this promising dataset, sonrotoclax in combination with zanubrutinib is being evaluated in patients with R/R MCL in the phase 3 CELESTIAL-RRMCL study (NCT06742996); enrollment is currently ongoing

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