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

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Introduction

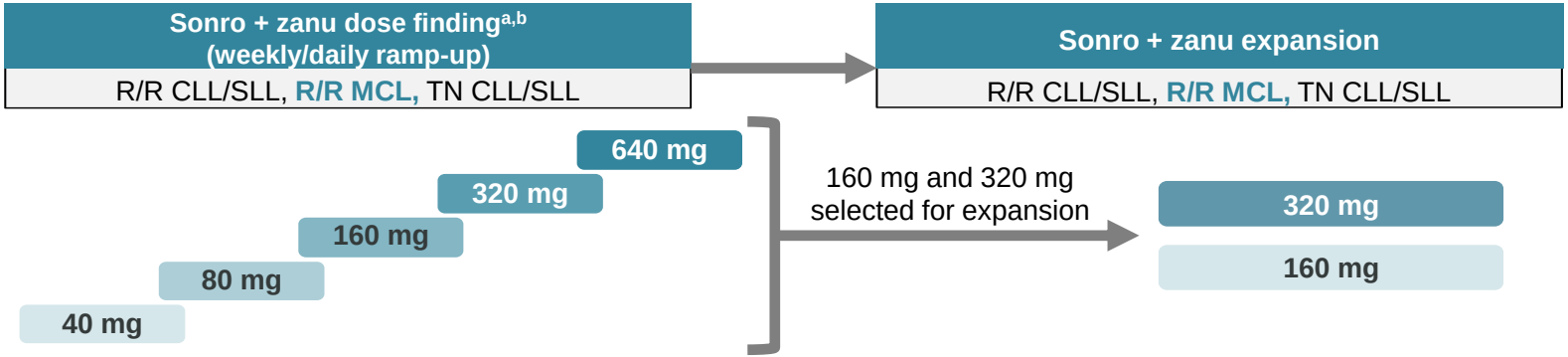
- Combining BCL2 and BTK inhibition with venetoclax + ibrutinib has efficacy in patients with R/R MCL, but is associated with high rates of toxicity and a need for a safer and potent combination still remains[1]
- Sonrotoclax (sonro; BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax with a shorter half-life and no accumulation[2]
- Zanubrutinib (zanu) is a next-generation BTK inhibitor approved globally for 5 indications, including R/R MCL[3]
- Zanu 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[4,5]
- Here, safety and efficacy data are presented for patients with R/R MCL treated with sonro + zanu in the ongoing BGB-11417-101 study

MCL, mantle cell lymphoma; R/R, relapsed/refractory.

1. Wang M, et al. ASH 2023. Abstract LBA-2; 2. Hu N, et al. AACR 2020. Abstract 3077; 3. Brukinsa. Prescribing information. BeiGene, Ltd; 2024; 4. Guo Y, et al. *J Med Chem.* 2019;62(17):7923-7940; 5. Tam CS, et al. *Expert Rev Clin Pharmacol.* 2021;14(11):1329-1344.

BGB-11417-101 (NCT04277637) Study Design

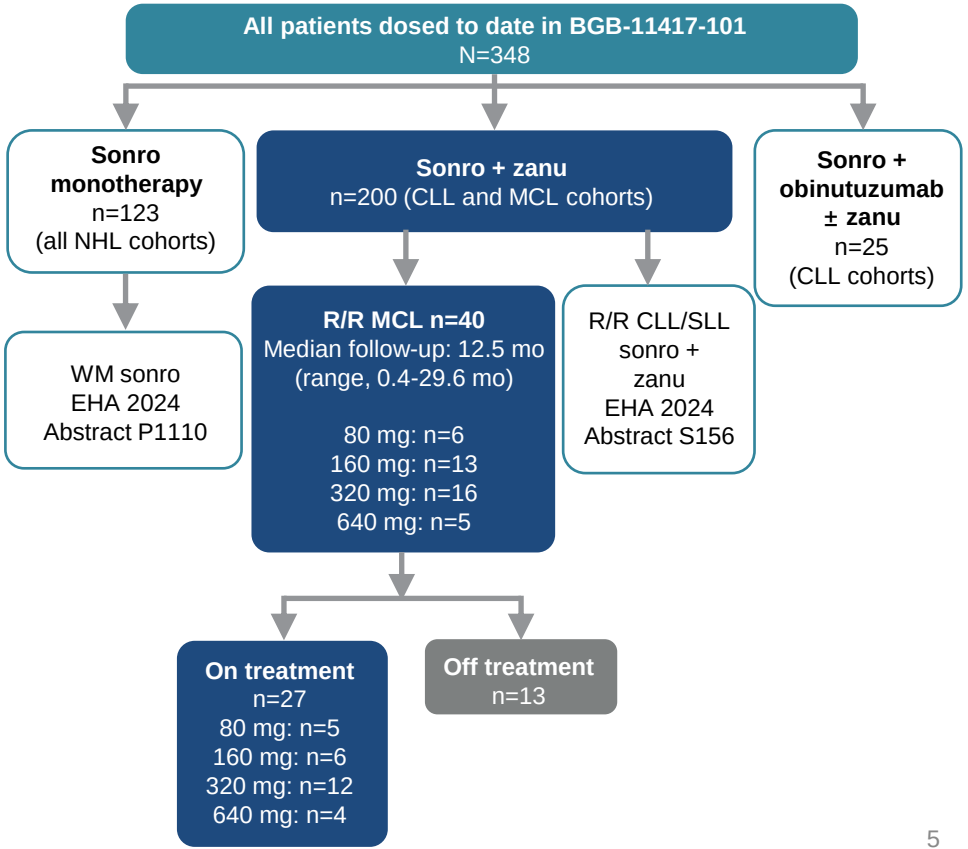
- First-in-human, phase 1, open-label, multicenter, dose-escalation and -expansion study in patients with B-cell malignancies
- Eligible patients: R/R MCL (disease that relapsed after or was refractory to ≥1 prior systemic therapy) and required treatment in the opinion of the investigator
- Primary objectives: assess safety/tolerability, evaluate the ramp-up dosing schedule, define MTD, and determine the RP2D of sonro in combination with zanu



[a] The safety monitoring committee reviewed dose-level cohort data before dose escalation. [b] Zanu was administered orally (320 mg QD or 160 mg BID) 8 to 12 weeks prior to sonro treatment; sonro was administered orally QD following a daily or weekly ramp-up schedule to mitigate potential risk of TLS.

Patient Disposition

- As of February 4, 2024, a total of 40 patients with R/R MCL received sonro + zanu and 27 remained on study treatment
  - 10 patients (25%) discontinued sonro + zanu due to PD (n=5), patient withdrawal (n=1), and AEs (n=4; 1 was treatment-related [pneumonia])
  - 4 patients discontinued zanu due to PD during lead-in (n=3) and 1 patient discontinued from zanu only due to diarrhea
- The sonro 160- and 320-mg dose levels were chosen for expansion cohorts



Baseline Patient Characteristics

Characteristic	Sonro 80 mg + zanu (n=6)	Sonro 160 mg + zanu (n=13)	Sonro 320 mg + zanu (n=16)	Sonro 640 mg + zanu (n=5)	All (N=40)
Study follow-up, median (range), months	27.5 (3.9-29.6)	16.0 (1.0-25.7)	12.5 (0.4-18.8)	3.5 (2.2-8.6)	12.5 (0.4-29.6)
Age, median (range), years	60.0 (46-84)	69.0 (45-81)	69.0 (45-85)	71.0 (68-80)	68.5 (45-85)
Male sex, n (%)	5 (83)	11 (85)	7 (44)	3 (60)	26 (65)
ECOG performance status, n (%)					
0	3 (50)	8 (62)	4 (25)	3 (60)	18 (45)
1	2 (33)	5 (38)	12 (75)	2 (40)	21 (53)
Tumor bulk, n (%)					
LDi <10 and ≥5 cm	3 (50)	4 (31)	3 (19)	2 (40)	12 (30)
LDi ≥10 cm	1 (17)	2 (15)	3 (19)	0	6 (15)
Ki67 ≥30%, n (%)	2 (33)	2 (15)	4 (25)	2 (40)	10 (25)
Prior therapy					
No. of lines of prior systemic therapy, median (range)	1 (1-1)	1 (1-4)	1 (1-3)	1 (1-1)	1 (1-4)
≥2 lines of prior systemic therapy, n (%)	0	3 (23)	5 (31)	0	8 (20)
Prior BTK inhibitor, n (%)	**0**	**0**	**3 (19)**	**0**	**3 (8)[a]**
BTK inhibitor as last prior therapy, n (%)	**0**	**0**	**3 (19)**	**0**	**3 (8)[a]**
Prior BTK inhibitor duration, median (range), months	–	–	4.8 (0.3-25.0)	–	4.8 (0.3-25.0)
Prior cellular therapies (transplant or CAR-T), n (%)	2 (33)	3 (23)	6 (38)	0	11 (28)

[a] Two patients discontinued due to toxicity.
CAR-T, chimeric antigen receptor T-cell; LDi, longest diameter.

TEAE Summary

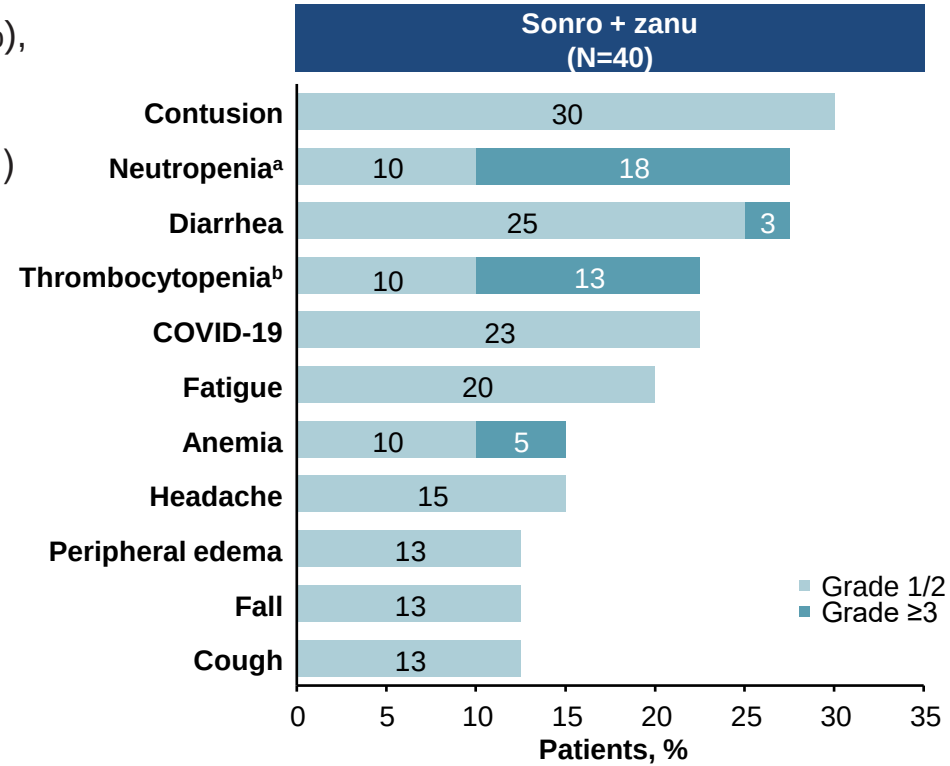
- Toxicity was generally the same among all tested dose levels with no new safety signals identified; sonro 160-mg and 320-mg dose levels were chosen for expansion cohorts

Patients, n (%)	Sonro 80 mg + zanu (n=6)	Sonro 160 mg + zanu (n=13)	Sonro 320 mg + zanu (n=16)	Sonro 640 mg + zanu (n=5)	All (N=40)
Any TEAE	4 (67)	13 (100)	15 (94)	5 (100)	37 (93)
Grade ≥3	4 (67)	6 (46)	7 (44)	1 (20)	18 (45)
Serious TEAEs	3 (50)	4 (31)	2 (13)	0	9 (23)
Leading to death	1 (17)	1 (8)	1 (6)	0	3 (8)[a]
Leading to zanu discontinuation	1 (17)	3 (23)	2 (13)	0	6 (15)[b]
Leading to zanu dose reduction	1 (17)	1 (8)	0	0	2 (5)[c]
Treated with sonro, n (%)	6 (100)	11 (85)	13 (81)	5 (100)	35 (88)
Leading to sonro discontinuation	0	3 (23)	2 (13)	0	5 (13)[d]
Leading to sonro dose reduction	0	0	0	0	0
Leading to death	0	1 (8)	0	0	1 (3)[e]

[a] Pleural effusion (due to PD), abdominal sepsis, and pneumonia. [b] Lymph node pain (due to PD), diarrhea, MDS, abdominal sepsis, pneumonia, and bruising. [c] COVID-19 (temporary).
[d] Diarrhea, abdominal sepsis, MDS, pneumonia and lymph node pain secondary to PD. [e] Pneumonia.
MDS, myelodysplastic syndrome; sonro, sonrotoclax; zanu, zanubrutinib.

TEAEs in ≥5 Patients by Grade

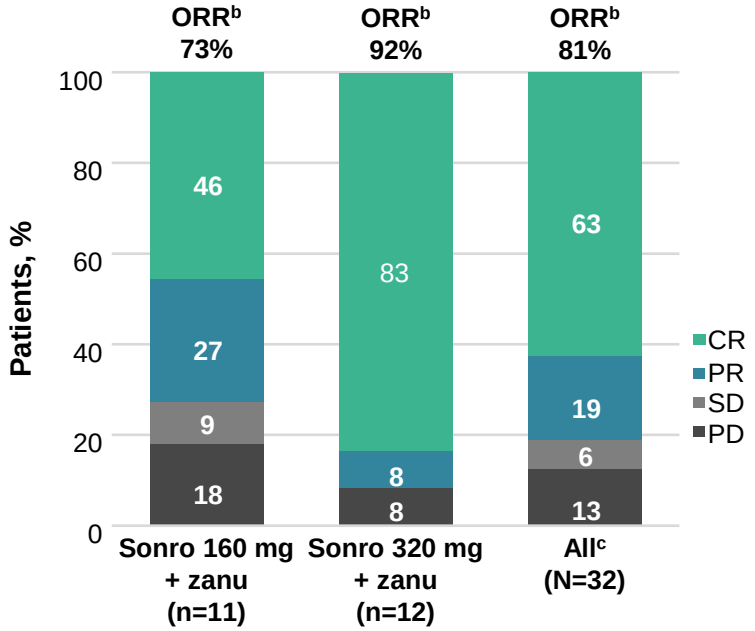
- Most common any-grade TEAEs: contusion (30%), neutropenia (28%), and diarrhea (28%)
- Most common grade ≥3 TEAE: neutropenia (18%)
  - Neutropenia was manageable, with:
    - No dose reductions
    - Only 1 dose hold due to concurrent COVID-19 infection
    - 6 patients used G-CSF (median duration = 3.5 days)
- No laboratory or clinical TLS
- Dose escalation completed with no MTD reached



[a] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

Treatment Response Rates[a]

- Median study follow-up was 12.5 months
  - ORRs were 73% and 92% in the 160- and 320-mg cohorts, respectively
  - CR rates were 46% and 83%, respectively



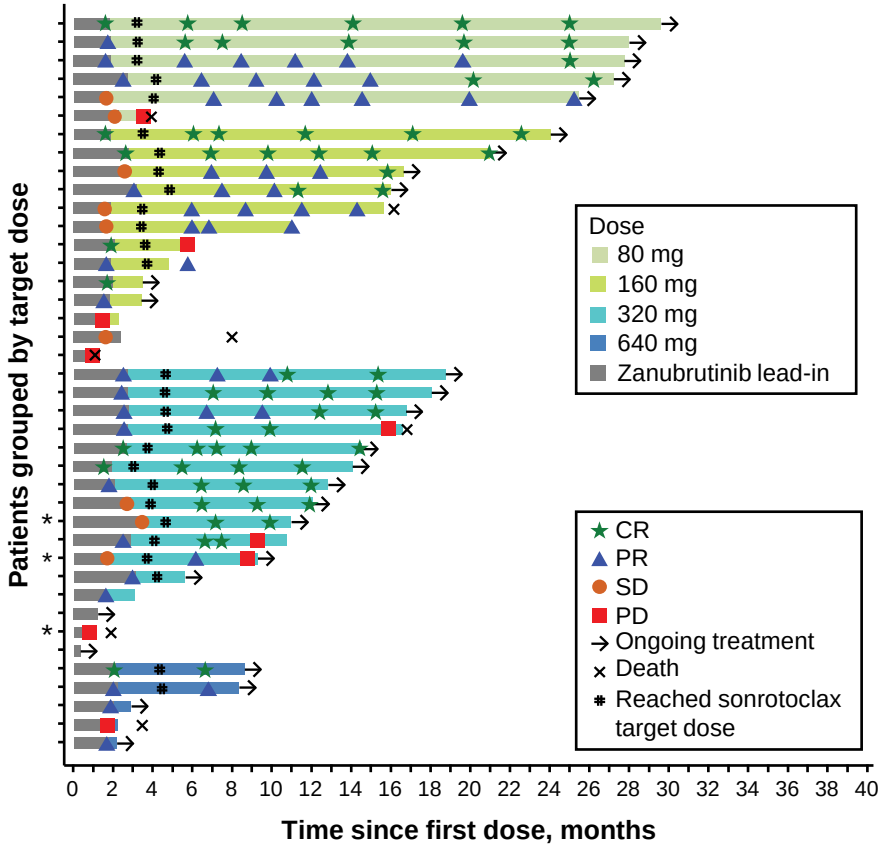
	Sonro 160 mg + zanu (n=11)	Sonro 320 mg + zanu (n=12)	All[c] (N=32)
Study follow-up[d], median (range), months	16.0 (1.0-25.7)	12.5 (0.4-18.8)	12.5 (0.4-29.6)

[a] Responses were assessed per Lugano 2014 criteria.[1] [b] ORR was defined as PR or better. [c] For all dose levels. [d] For all patients as treated (N=40).

1. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-3068.

Treatment Duration and Investigator-Assessed Responses[a]

- Of 3 response-evaluable patients with prior BTK inhibitor treatment, 2 responded: 1 PR and 1 CR



* Patient had prior treatment with BTK inhibitor.
[a] Gray bar indicates duration of zanu lead-in.

Conclusions

- Sonrotoclax in combination with zanubrutinib was generally well tolerated
  - The maximum tolerated dose was not reached up to the highest assessed dose of 640 mg
  - No atrial fibrillation or TLS (laboratory or clinical) events were observed
- Sonrotoclax + zanubrutinib combination therapy demonstrated deep responses in patients with R/R MCL, including an ORR of 92% and CR rate of 83% in the 320-mg cohort
- The 320-mg dose was selected as RP2D for development in future pivotal studies

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