Phase 1 Study With the Novel BCL2 Inhibitor Sonrotoclax (BGB-11417) as Monotherapy or in Combination With Zanubrutinib for NHL or Waldenström Macroglobulinemia (WM): Preliminary Data

Poster #PO-268

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INTRODUCTION

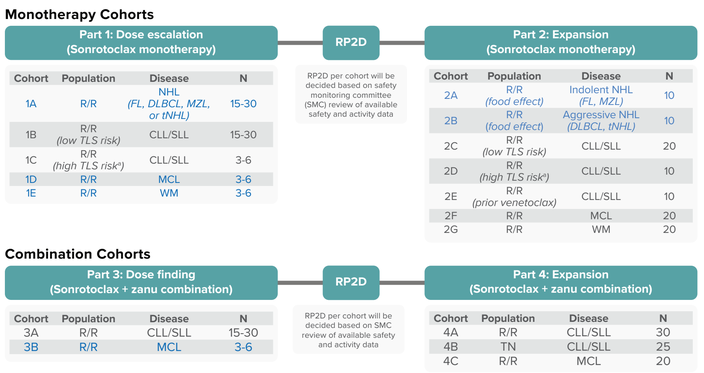
- Sonrotoclax (BGB-11417) is a BCL2 inhibitor and key regulator of apoptosis, aberrantly expressed in many hematologic malignancies[1]
  - The currently approved BCL2 inhibitor, venetoclax, has been shown to be safe and effective and is approved for the treatment of patients with CLL/SLL and AML[2,3]
  - Treatment with venetoclax can be limited by common GI toxicities, neutropenia, and the emergence of specific *BCL2* mutations around the BH3-binding groove[4]
- Sonrotoclax was developed as a potent and highly selective inhibitor of BCL2[5]
  - Sonrotoclax inhibits BCL2 in vitro with an IC_{50} of 0.01 nM compared to 0.20 nM for venetoclax
  - Antitumor activity of sonrotoclax appears to be more potent than venetoclax in human ALL and MCL cell lines and in xenograft mouse models of DLBCL[6]
  - Sonrotoclax has a favorable PK profile with excellent bioavailability and selectivity for BCL2
  - Toxicology studies have shown sonrotoclax to have a broad therapeutic index and tolerable safety profile[7]
- Zanubrutinib (zanu) is a next-generation BTK inhibitor that has activity and favorable toxicity/tolerability and has been approved for the treatment of patients with CLL/SLL, MCL, MZL, and WM in the US or the EU[8-14]
- Zanu achieved superior PFS vs ibrutinib in a final analysis of the phase 3 ALPINE trial with less atrial fibrillation and a favorable safety profile[15]
- The combination of ibrutinib with venetoclax in patients with R/R MCL or TN CLL/SLL appears to be effective, but the side-effect profile can be problematic, with high rates of dose reductions and discontinuations[16,17]
- Here, we report preliminary results of the BGB-11417-101 trial (NCT04277637) in patients with NHL, including separate cohorts for MCL and WM, treated with either sonrotoclax monotherapy or in combination with zanu

METHODS

Study Design

- BGB-11417-101 is a first-in-human phase 1, open-label, multicenter, dose escalation and expansion study
- Disease-specific dose escalation cohorts were followed by the corresponding expansion cohorts:
  - Sonrotoclax monotherapy cohorts (parts 1 and 2)
  - Sonrotoclax in combination with zanu cohorts (parts 3 and 4)
- Eligible patients included those with various B-cell malignancies
- Dose escalation investigated up to 5 potential dose levels of sonrotoclax (40, 80, 160, 320, or 640 mg QD) before establishing RP2D
- AEs were reported per CTCAE v5.0
- Response to treatment was assessed by Lugano classification for patients with NHL and Owen criteria for patients with WM[18,19]

Figure 1. Study Design



Blue text indicates cohorts presented in this poster.
[a]High TLS risk defined as the presence of any lymph node ≥10 cm or the presence of any lymph node ≥5 cm with concurrent absolute lymphocyte count ≥25×10⁹/L.

Dosing and Dose Escalation

- Sonrotoclax dosed QD ≤30 minutes after a low-fat meal
- For combination therapy, zanu (160 mg BID or 320 mg QD) started 8-12 weeks (depending on tumor burden) before starting sonrotoclax
- Starting target dose level for a cohort may be >40 mg if established as safe in other cohorts per SMC

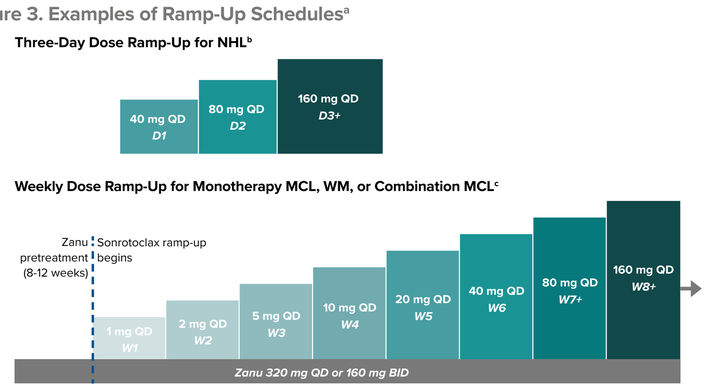
Figure 2. Dosing and Dose Escalation

[a]SMC review of dose-level cohort data before dose escalation.

TLS Prophylaxis

- To mitigate potential TLS, all patients received a dose ramp-up to the target dose (**Figure 3**)
  - Patients with NHL (excluding MCL and WM) received a 3-day ramp-up, with daily dose increases (25%, 50%, and 100% of the target dose during days 1-3)
  - Patients with MCL or WM received weekly dose increases, beginning with 1 mg QD then doubling until the target dose was reached
  - Required hospitalization at first 3 visits for ramp-up dose (no longer required)
- Other TLS prophylaxis
  - Hydration: oral or intravenous 1.5-2 L/day from ≥1 day before until ≥1 day after each new dose level
  - Antihyperuricemics (allopurinol or rasburicase): from ≥2 days before first dose until 1 week after reaching final target dose level
  - TLS laboratory results and PK monitored frequently at select time points

Figure 3. Examples of Ramp-Up Schedules[a]



[a]Ramp-up will depend on target dose: examples show 160 mg target dose. [b]Three-day ramp-up doses vary depending on target dose: D1 25%, D2 50%, D3+ 100%. [c]Weekly ramp-up target doses follow the same weekly ramp-up schedule, stopping once they reach the target dose (lower target dose = shorter ramp-up). Ramp-up is identical for monotherapy.

RESULTS

Figure 4. Patient Disposition

Data cutoff: 1 September 2022.

[a]Includes DLBCL (n= 18), FL (n=6), MZL (n=7), MCL (n=3). [b]Includes other or physician decision. [c]Patients who are still in the zanu pretreatment phase and have not yet received sonrotoclax. [d]One patient progressed on zanu pretreatment before receiving sonrotoclax.

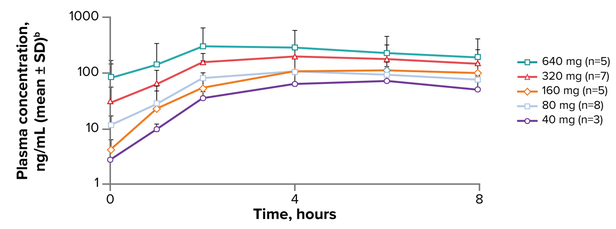
Table 1. Patient Characteristics

Characteristic	Sonrotoclax monotherapy (n=43)	Sonrotoclax + zanu (n=16)	All patients (N=59)
Median age (range), years	71 (48-86)	62 (45-85)	70 (45-86)
Sex, n (%)			
Male	30 (70)	12 (75)	42 (71)
Female	13 (30)	4 (25)	17 (29)
ECOG PS, n (%)			
0	18 (42)	7 (44)	25 (42)
1	22 (51)	8 (50)	30 (51)
2	3 (7)	0	3 (5)
Unknown	0	1 (6)	1 (2)
Disease type, n (%)			
DLBCL	18 (42)	0	18 (31)
FL	6 (14)	0	6 (10)
MZL	7 (16)	0	7 (12)
MCL	5 (12)	16 (100)	21 (36)
WM	9 (21)	0	9 (15)
Median no. of prior lines of therapy	2 (1-8)	1 (1-3)	2 (1-8)
Median time from end of most recent systemic therapy to first dose (range), months	3.1 (0-158)	15.9 (3-64)	8.5 (0-158)

All enrolled patients were R/R.

- Preliminary steady-state PK data from patients with NHL or CLL who received sonrotoclax monotherapy at 40 to 640 mg target doses QD for 3 weeks
  - Dose-dependent PK from 40 to 640 mg
  - Fast absorption (median T_{max}~4 hours)
  - Short half-life (median $T_{½}$~5 hours)
  - No significant accumulation at steady state
  - Similar PK with and without zanu

Figure 5. Steady-State PK[a]



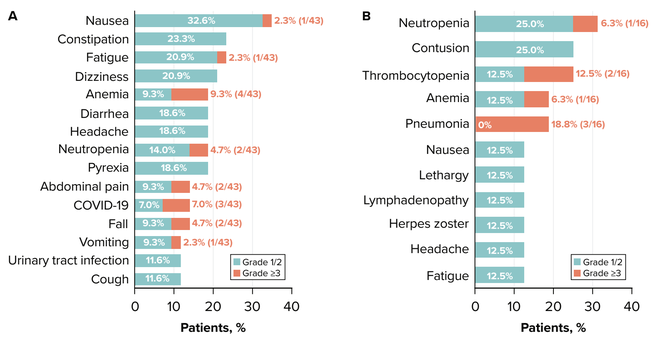
[a]PK data were pooled from all study cohorts, not just CLL. [b]Mean ±SD steady-state sonrotoclax plasma concentration profile for 40-640 mg QD in patients with NHL and CLL who received sonrotoclax monotherapy (combination PK not shown here) SD, standard deviation.

Table 2. Overall Adverse Events and Dose Modifications Regardless of Attributions

Adverse events, n (%)	Sonrotoclax monotherapy (n=43)	Sonrotoclax + zanu (n=16[a])
Any AEs	40 (93)	13 (81)
Grade ≥3 AE	20 (47)	6 (38)
Serious AE	17 (40)	5 (31)
Leading to death	3 (7)[b]	2 (13)[c]
Treated with sonrotoclax	43	10
Leading to hold of sonrotoclax	9 (21)[d]	4 (40)[e]
Leading to dose reduction of sonrotoclax	1 (2)[f]	0
Leading to discontinuation of sonrotoclax	2 (5)[g]	0

[a]All patients on combination therapy have MCL; Includes 6 patients who have only received zanu. [b]Gastrointestinal hemorrhage, COVID-19 pneumonia death secondary to progression. [c]Cardiac arrest (not drug related), pleural effusion. [d]Pneumonia, sepsis, vomiting, CMV reactivation, worsening nausea, febrile neutropenia, COVID-19 pneumonia, ALT increased, AST increased, GGT increased, small intestinal obstruction, GI hemorrhage, platelet count decreased, diverticulitis, COVID-19, neutropenia. [e]Diarrhea, pneumonia, pleural effusion, lymph node pain, lymphadenopathy. [f]Gingival pain, fatigue, weight loss. [g]COVID-19 pneumonia; GI hemorrhage.

Figure 6. Adverse Events in ≥10% of Patients in (A) Monotherapy and (B) Combination Cohorts[a]



[a]Includes n=6 patients who are still in zanu pretreatment phase and have not yet received sonrotoclax; All patients who received combination therapy have MCL.

Selected Adverse Events

- A single case of laboratory **TLS** was observed in a patient with MZL (640 mg target dose level: food-effect cohort)
  - Elevated phosphate, urate, and potassium
  - Occurred after first dose of 160 mg, which was given 7 days before day 1 as part of food effect evaluation
  - Circulating tumor cells and spleen normalized within 24 hours after first dose
  - Patient was hydrated and the laboratory changes resolved within 24 hours; received full dosing as planned from day 1 with no recurrence of TLS
- **GI toxicity** was the most common monotherapy toxicity, but all cases were mild with grade ≥3 nausea or vomiting seen in only 1 patient each (**Figure 5**)
  - Diarrhea mostly grade 1, with grade 2 observed in 2 patients
- **Neutropenia** was the most common toxicity (combination therapy) or hematologic toxicity (monotherapy), but was typically mild with grade ≥3 seen in 2 patients who received monotherapy and 1 patient who received combination therapy (**Figure 5**)
  - Febrile neutropenia occurred in 2 patients on monotherapy; no events were observed in patients who received combination therapy
  - Among 12 patients who received G-CSF (median course 3-days), 3 received >1 course of the therapy during treatment

Dose-Limiting Toxicities

- Only 1 DLT of febrile neutropenia noted among patients with NHL (**Table 3**)
- DLT occurrence was not dose dependent, and zanu combination did not appear to increase its risk
- Findings are consistent with previous sonrotoclax CLL data, which has reviewed up to 320 mg so far with no MTD reached

Table 3. Dose-Limiting Toxicities

DLTs, n/N	40 mg	80 mg	160 mg	320 mg	640 mg
Sonrotoclax (NHL)	0/3	0/4	1/4	0/9	0/6
Sonrotoclax (WM)	-	0/5	TBD	TBD	TBD
Sonrotoclax + zanu (MCL)	-	0/5	0/3	TBD	TBD

- Patient response to therapy is presented in **Table 4** along with the change in SPD in patients with NHL and treatment duration in **Figures 5** and **6**
- NHL (R/R monotherapy)
  - Significant reductions in SPD from baseline were noted in most patients
  - Disease control (CR+PR+SD) in 10 of 28 (36%) patients: 2 PRs at 160 and 640 mg and 1 CR at 320 mg
- WM (R/R monotherapy)
  - Follow-up was limited; however, 3 of 7 (43%) patients with at least 1 assessment reached PR at 80 mg
- MCL (R/R combination)
  - Response in 7 of 10 (70%) patients with at least 1 assessment
  - At 80 mg, 4 of 6 (67%) patients achieved CR
  - At 160 mg, 2 of 4 (50%) patients achieved CR and 1 reached PR

Table 4. Efficacy of Sonrotoclax as Monotherapy and in Combination With Zanu

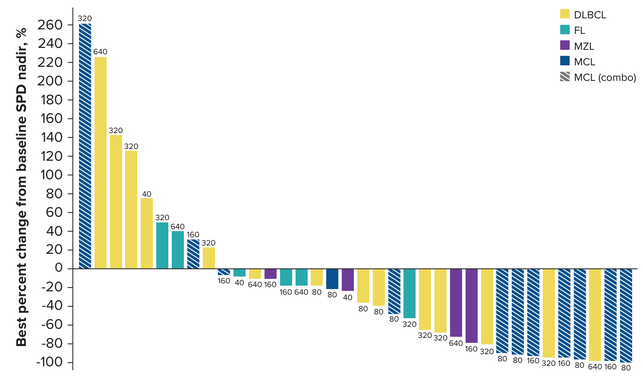
Response, n (%)	Sonrotoclax monotherapy (n=43)		Sonrotoclax + zanu combination (n=16)
	R/R NHL, DLBCL, MZL, FL, tFL, MCL (n=34)[a]	R/R WM (n=9)[b]	R/R MCL (n=16)[c]
Treated with sonrotoclax	34	9	10
Efficacy evaluable	29[d]	7	9
Best overall response,[e]	3 (10)	3 (43)	7 (78)
CR	1 (3)	0	6 (67)
PR	2 (7)	3 (43)	1 (14)
SD	7 (24)	2 (29)	0
PD	18 (62)	1 (14)	2 (22)
Discontinued before assessment	1 (3)	1 (14)	0
Follow-up, months (range)	7 (0.1-29)	6 (2-10)	5 (1-13)

[a]At 40 mg: n=3; 80 mg: n=7; 160 mg: n=4; 320 mg: n=9; 640 mg: n=11. [b]At 80 mg: n=6; 160 mg: n=3. [c]At 80 mg: n=12; 160 mg: n=4. [d]One patient with MCL on monotherapy was efficacy evaluable. [e]PR or better.

CONCLUSIONS

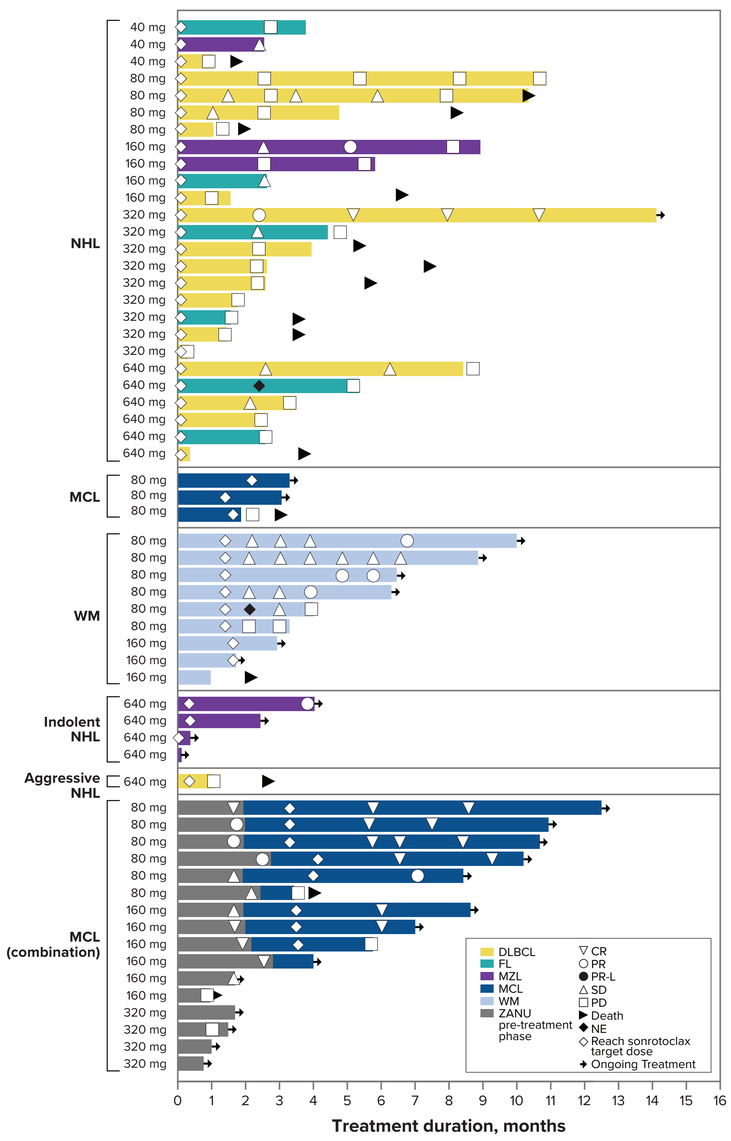
- Sonrotoclax is tolerable in patients with NHL or WM at doses up to 640 mg
  - For patients with NHL on monotherapy, there was only 1 DLT and MTD was not reached
  - Sonrotoclax in combination with zanu was also well tolerated at doses of sonrotoclax ≤320 mg, with dose escalation ongoing in patients with MCL
  - No clinical TLS was observed; there was 1 case of laboratory TLS that was resolved within 24 hours
- These data demonstrate the preliminary efficacy of sonrotoclax monotherapy (NHL, WM) and with zanu (MCL), with more responses observed at higher dose levels
- The study continues to determine RP2D in monotherapy and combination therapy

Figure 7. Change in SPD Among Patients With NHL and MCL[a]



[a]All patients had at least 1 postbaseline scan result.

Figure 8. Duration of Treatment and Response[a]



[a]Safety analysis set.
All received treatments were monotherapy except patients in part 3B, which were combo MCL.

ABBREVIATIONS

AE, adverse event; ALL, acute lymphoblastic leukemia; ALT, alanine transaminase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; BCL2, B-cell lymphoma 2; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; D, day; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GGT, gamma-glutamyltransferase; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; IC, inhibitory concentration; MCL, mantle cell lymphoma; MTD, minimum tolerated dose; MZL, marginal zone lymphoma; NE, not evaluable; NHL, non-Hodgkin lymphoma; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; QD, daily; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SD, stable disease; SLL, small lymphocytic lymphoma; SMC, safety monitoring committee; SPD, sum of the product of the diameters; $T_{½}$, half-life; tFL, transformed FL; TBD, to be determined; TLS, tumor lysis syndrome; T_{max}, maximum time; TN, treatment naïve; tNHL, transformed NHL; W, week; WM, Waldenström macroglobulinemia; zanu, zanubrutinib.

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DISCLOSURES

EGB: consulting for Janssen, AbbVie, Kiowa, EUSA, BeiGene; honoraria from Janssen, AbbVie, Takeda, EUSA, AstraZeneca; travel expenses from Janssen, AbbVie, Roche; **JDS:** consulting for AbbVie, AstraZeneca, BeiGene, Biogen, BMS, Roche, TG Therapeutics, Verastem; research funding from Adaptive Biotechnologies, BeiGene, BostonGene, Genentech/Roche, GSK, MEI Pharma, Moderna, TG Therapeutics; **ML:** travel expenses from Celgene; education support from Janssen; **SO:** consulting for AbbVie, Antengene, AstraZeneca, BeiGene, BMS, CSL Behring, Gilead, Merck, Novartis, Janssen, Roche, Takeda; research funding from AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Janssen, Merck, Novartis, Pharmacyclics, Roche, Takeda; honoraria from AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Janssen, Merck, Novartis, Roche, Takeda; advisory board for AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Janssen, Merck, Novartis, Roche, Takeda; **CYC:** consulting for Roche, Janssen, MSD, Gilead, AstraZeneca, Lilly, TG Therapeutics, BeiGene, Novartis, BMS; research funding from BMS, Roche, AbbVie; honoraria from Roche, Janssen, MSD, Gilead, AstraZeneca, Eli Lilly, TG Therapeutics, BeiGene, Novartis, BMS; advisory board for Roche, Janssen, MSD, Gilead, AstraZeneca, Lilly, TG Therapeutics, BeiGene, Novartis, BMS; **HC:** speakers bureau for Janssen, Roche; advisory committee for Janssen, Abbvie, Eusa, GSK; travel expenses from Amgen, Celgene; **EV:** research funding from Janssen; **AT:** consulting for BeiGene, AstraZeneca, AbbVie, Janssen; honoraria from BeiGene, AstraZeneca, Janssen, AbbVie; speaker's bureau for BeiGene, AstraZeneca, Janssen, AbbVie; **JH, YF, and DS:** employed and stock with BeiGene; **DS:** employed by and stock with and travel expenses from BeiGene; **CST:** honoraria from Janssen, AbbVie, BeiGene, Loxo Oncology, AstraZeneca; research funding from AbbVie, Janssen, BeiGene.

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