A Phase 1 Study With the Novel B-Cell Lymphoma 2 (BCL2) Inhibitor Sonrotoclax (BGB-11417) as Monotherapy or in Combination With Zanubrutinib in Patients With CLL/SLL: Preliminary Data

Chan Y. Cheah[1-3], Constantine S. Tam[4,5], Masa Lasica[6], Emma Verner[7,8], Peter J. Browett[9], Mary Ann Anderson[10,11], James Hilger[12], Yiqian Fang[12], David Simpson[12], Stephen Opat[6,13]

[1]Department of Haematology, Sir Charles Gairdner Hospital and PathWest Laboratory Medicine, Nedlands, WA, Australia; [2]Medical School, University of Western Australia, Crawley, WA, Australia; [3]Linear Clinical Research, Nedlands, WA, Australia; [4]Alfred Hospital, Melbourne, VIC, Australia; [5]Monash University, Clayton, VIC, Australia; [6]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [7]Concord Repatriation General Hospital, Concord, NSW, Australia; [8]University of Sydney, Sydney, NSW, Australia; [9]Department of Haematology, Auckland City Hospital, Auckland, New Zealand; [10]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [11]Division of Blood Cells and Blood Cancer, The Walter and Eliza Hall Institute, Parkville, VIC, Australia; [12]BeiGene (Shanghai) Co., Ltd., Shanghai, China and BeiGene USA, Inc., San Mateo, CA, USA; [13]Monash Health, Clayton, VIC, Australia

INTRODUCTION

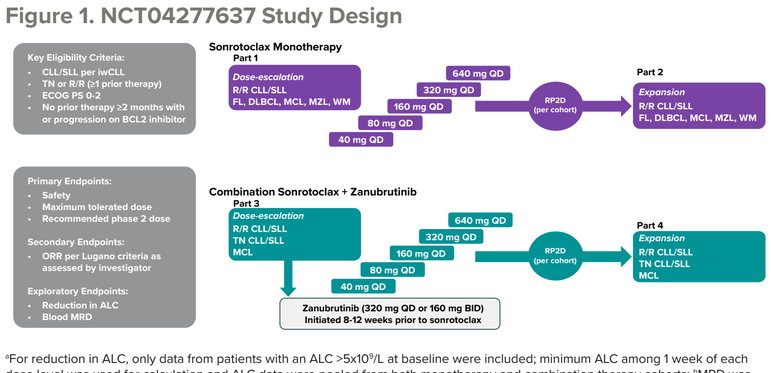
- BCL2 inhibition is an established mechanism for treating B-cell malignancies such as chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1,2]
- The combination of inhibitors of BCL2 (BCL2i) and Bruton tyrosine kinase (BTKi) has potent activity in CLL and mantle cell lymphoma (MCL)[3-6]
- Ibrutinib with venetoclax in patients with CLL/SLL appears to be effective; however, adverse events (AEs) may limit their use, leaving an unmet need for a safe and efficacious BTKi + BCL2i combination regimen[7]
- Sonrotoclax (BGB-11417) has shown more potent and selective BCL2 inhibition and better activity against tumors with *BCL2* mutations than venetoclax in vitro[2]
  - Sonrotoclax has a 14x higher affinity for BCL2 than venetoclax; additionally, sonrotoclax has a relative selectivity for BCL-xL that is 6x lower than venetoclax
- Zanubrutinib, a next-generation BTK inhibitor, has demonstrated superior efficacy and favorable safety, especially cardiovascular, in head-to-head studies with ibrutinib in CLL[8]
- Here, preliminary data are presented from a phase 1 study of sonrotoclax as monotherapy or in combination with zanubrutinib in patients with CLL/SLL

METHODS

Study Design

- BGB-11417-101 (NCT04277637) is a first-in-human, phase 1, multicenter study in patients with B-cell malignancies; the study design for the CLL/SLL cohorts is shown in **Figure 1**

Figure 1. NCT04277637 Study Design

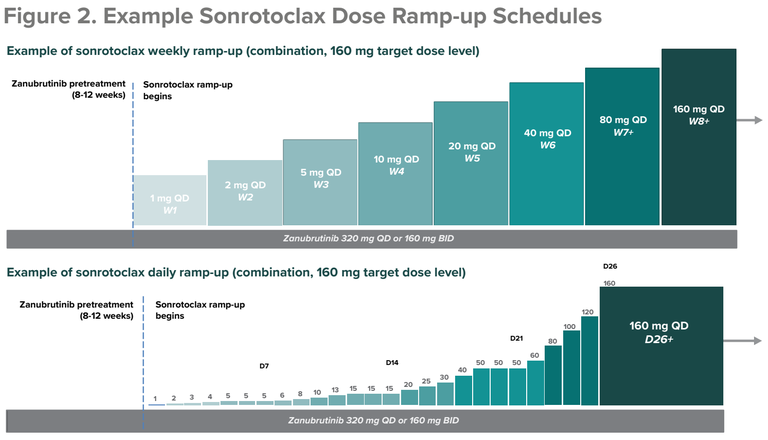


[a]For reduction in ALC, only data from patients with an ALC >5x10^9/L at baseline were included; minimum ALC among 1 week of each dose level was used for calculation and ALC data were pooled from both monotherapy and combination therapy cohorts; [b]MRD was measured by ERIC flow cytometry with 10^{-4} sensitivity.
ALC, absolute lymphocyte count; BCL2, B-cell lymphoma 2; BID, twice daily; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ERIC, European Research Initiative on CLL; iwCLL, International Workshop on CLL; MRD, minimal residual disease; ORR, overall response rate; QD, every day; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive; ULN, upper limit of normal.

Dose Ramp-up

- To mitigate potential tumor lysis syndrome (TLS), all patients received either a weekly or daily dose ramp-up to the sonrotoclax target dose (**Figure 2**)
- TLS prophylaxis also included hydration starting 24-48 hours prior to first dose, allopurinol starting 2-3 days prior to first dose, and rasburicase as indicated

Figure 2. Example Sonrotoclax Dose Ramp-up Schedules

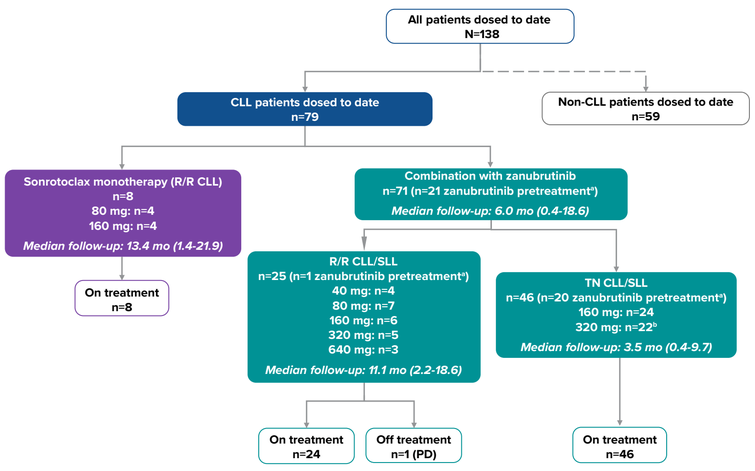


BID, twice daily; D, day; QD, once daily; W, week.

RESULTS

- As of September 1, 2022, 79 patients with CLL/SLL received either sonrotoclax as monotherapy (n=8) or in combination with zanubrutinib (n=71; **Figure 3**)

Figure 3. Patient Disposition



Data cutoff date: September 1, 2022. [a]Patients in the zanubrutinib pretreatment phase who have not yet received sonrotoclax; [b]All patients were assigned to a weekly ramp-up schedule except for n=4 TN patients (320 mg dose level).
CLL, chronic lymphocytic leukemia; mo, month; PD, progressive disease; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive.

- The overall study population had a median age of 62 years and 79% of patients were male (**Table 1**)
- Del(17p) and *TP53* mutation were found in 17% and 23% of patients, respectively

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Sonrotoclax monotherapy (n=8)	Sonrotoclax + zanubrutinib (n=71)	All patients (N=79)
Median age, (range), years	68.5 (55-84)	61.0 (35-84)	62.0 (35-84)
Sex, n (%)			
Male	6 (75.0)	56 (78.9)	62 (78.5)
Female	2 (25.0)	15 (21.1)	17 (21.5)
ECOG PS, n (%)			
0	3 (37.5)	49 (69.0)	52 (65.8)
1	5 (62.5)	21 (29.6)	26 (32.9)
2	0	1 (1.4)	1 (1.3)
Disease type, n (%)			
CLL	8 (100)	70 (99)	78 (99)
SLL	0	1 (1)	1 (1)
R/R, n (%)	8 (100)	25 (35.2)	33 (41.8)
Number of prior lines of therapy, median (range)	2 (1-3)	1 (1-2)	1 (1-3)
Time from end of most recent systemic therapy to first dose, median (range), months	0.4 (0.0-10.2)	57.0 (1.6-194.4)	45.4 (0.0-194.4)
TN, n (%)	0	46 (64.8)	46 (58.2)
Risk status, n (%)			
del(17p)	2 (25)	11 (15.5)	13 (16.5)
TP53^{mut}	3 (37.5)	15 (21.1)	18 (22.8)

CLL, chronic lymphocytic leukemia; del(17p), deletion in chromosome 17p; ECOG, Eastern Cooperative Oncology Group Performance Status; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive; *TP53*^{mut}, mutation of p53.

Safety

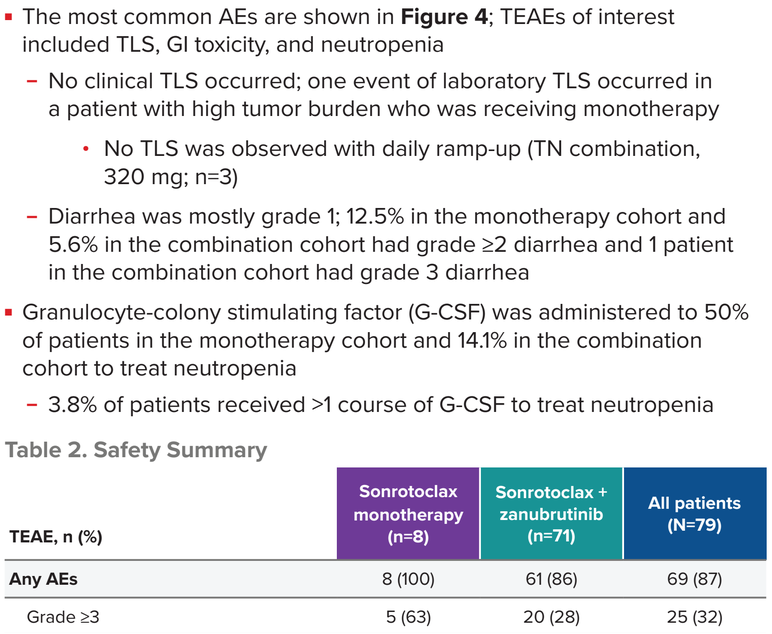
- Toxicity did not seem dose dependent; only 1 DLT (febrile neutropenia) occurred among patients receiving monotherapy (80 mg) and no DLTs have been observed to date with combination therapy at any dose level (**Table 2**)
- No AEs leading to death or sonrotoclax discontinuation occurred in any patients
- The most common AEs are shown in **Figure 4**; TEAEs of interest included TLS, GI toxicity, and neutropenia
  - No clinical TLS occurred; one event of laboratory TLS occurred in a patient with high tumor burden who was receiving monotherapy
    - No TLS was observed with daily ramp-up (TN combination, 320 mg; n=3)
  - Diarrhea was mostly grade 1; 12.5% in the monotherapy cohort and 5.6% in the combination cohort had grade ≥2 diarrhea and 1 patient in the combination cohort had grade 3 diarrhea
- Granulocyte-colony stimulating factor (G-CSF) was administered to 50% of patients in the monotherapy cohort and 14.1% in the combination cohort to treat neutropenia
  - 3.8% of patients received >1 course of G-CSF to treat neutropenia

Table 2. Safety Summary

TEAE, n (%)	Sonrotoclax monotherapy (n=8)	Sonrotoclax + zanubrutinib (n=71)	All patients (N=79)
Any AEs	8 (100)	61 (86)	69 (87)
Grade ≥3	5 (63)	20 (28)	25 (32)
Serious AEs	2 (25)	7 (10)	9 (11)
Treated with sonrotoclax	8	50	58
Leading to hold of sonrotoclax	5 (62.5)	14 (28)	19 (33)
Leading to dose reduction of sonrotoclax	0	1 (2)	1 (2)

AE, adverse event; TEAE, treatment-emergent adverse event.

Figure 4. Most Frequent AEs



[a]Includes 21 patients who were still in the zanubrutinib pretreatment phase and had not yet receivedsonrotoclax; [b]Includes 46 patients who were TN.
ALT, alanine aminotransferase; COVID-19, coronavirus disease of 2019; GERD, gastroesophageal reflux disease; TN, treatment-naive; URTI, upper respiratory tract infection.

CONCLUSIONS

- Sonrotoclax, alone or in combination with zanubrutinib, was well tolerated in patients with TN or R/R CLL/SLL
  - Dose escalation continues to 640 mg with only 1 DLT; Grade ≥3 neutropenia and grade ≥2 diarrhea were uncommon and manageable
  - Only 1 event of laboratory TLS was seen; TLS was mitigated by the prophylactic measures and ramp-up schedule
  - The AEs observed in this trial were consistent with those observed in a sonrotoclax study in patients with NHL[9], in which doses up to 640 mg were tested and no MTD was reached
- Promising efficacy was seen with sonrotoclax as monotherapy and in combination with zanubrutinib in both TN and R/R CLL/SLL
- Based on ALC reduction, sonrotoclax may be ~5X as potent as venetoclax by dose
- MRD data are preliminary but appear promising
- A cohort of venetoclax-treated patients with CLL/SLL is currently recruiting

Efficacy

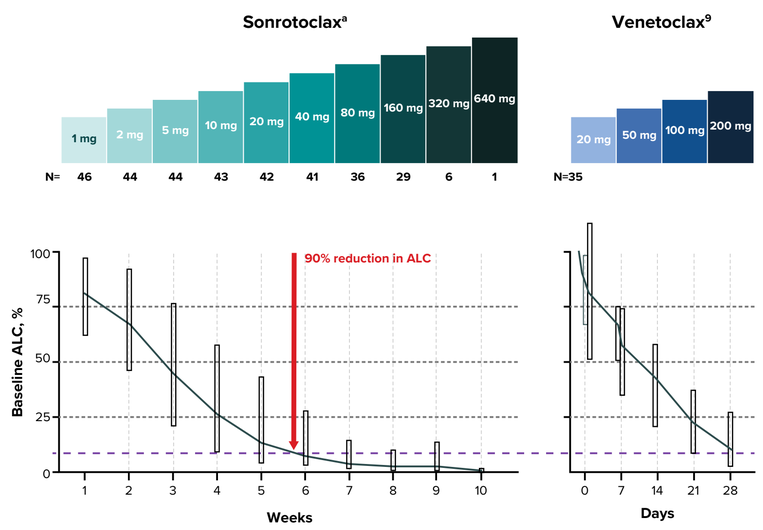
- With a median follow-up of 13.4 months in the sonrotoclax monotherapy cohort and 11.1 months in the sonrotoclax combination cohort, patients with R/R CLL/SLL had an ORR of 67% and 95%, respectively (**Table 3**)

Table 3. ORR

Parameter	Sonrotoclax monotherapy R/R (n=8)	Sonrotoclax + zanubrutinib	
		R/R (n=25)	TN (n=46)
Treated with sonrotoclax	8	24	26
Efficacy-evaluable	6	20a	11a
ORR	4 (67)	19 (95)	11 (100)
CR	2 (33)	6 (30)	2 (18)
PR	2 (33)	13 (65)	9 (82)
SD	2 (33)	1 (5)	0
PD	0	0	0
Median follow-up, months (range)	13.4 (1.4-21.9)	11.1 (2.2-18.6)	3.5 (0.4-9.7)

[a]n=2 (R/R) and n=11 (TN) responded after zanubrutinib pretreatment but have not yet had response assessment on combination treatment: they are not included here. CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naive.

Figure 5. Reduction in Absolute Lymphocyte Counts



Only data from patients with an ALC >5x10^9/L at baseline were included. Box plots represent median and 10th-90th percentiles.
[a]Minimum ALC among 1 week of each dose level was used for calculation. N represents the number of patients who completed weekly dosing at the dose level underneath. ALC data were pooled from both monotherapy (n=7) and combination therapy (n=39) cohorts because no difference was observed.
ALC, absolute lymphocyte count.

REFERENCES

1. Kapoor I, et al. *Cell Death Dis*. 2020;11(11):941.
2. Hu N, et al. AACR 2020. Abstract 3077.
3. Soumerai JD, et al. *Lancet Haematol*. 2021;8(12):e879-e890.
4. Hillmen P, et al. *J Clin Oncol*. 2019;37(30):2722-2729.
5. Jain N, et al. *N Engl J Med*. 2019;380(22):2095-2103.
6. Wierda WG, et al. *J Clin Oncol*. 2021;39(34):3853-3865.
7. Kater AP, et al. *NEJM Evid*. 2022;1(7) doi: 10.1056/EVIDoa2200006
8. Brown JR, et al. SOHO 2022. Abstract CLL-115.
9. Roberts AW, et al. *N Engl J Med*. 2016;374(4):311-322.

DISCLOSURES

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; **CST:** honoraria from Janssen, AbbVie, BeiGene, Loxo Oncology, AstraZeneca; research funding from AbbVie, Janssen, BeiGene; **ML:** travel expenses from Celgene; education support from Janssen; **EV:** research funding from Janssen; **PJB:** honoraria from AbbVie, Arrowhead, MSD; research funding from BeiGene, Roche; advisory board for Eysa Pharma, Janssen; **MAA:** honoraria from Gilead, CSL, Novartis, Takeda, Janssen, AbbVie, AstraZeneca; employee of the Walter and Eliza Hall Institute; **JH, YF, DS:** employee of and owns stock in BeiGene; **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.

ACKNOWLEDGMENTS

We would like to thank the investigators, site support staff, and especially the patients for participating in this study. This study was sponsored by BeiGene. Editorial support was provided by Medical Expressions and funded by BeiGene.

CORRESPONDENCE

Chan Y. Cheah
chan.cheah@health.wa.gov.au

Presented at Blood 2023; November 5-8, 2023; Melbourne, Australia