Primary Analysis Results of Novel BCL2 Inhibitor Sonrotoclax (BGB-11417) Monotherapy in Patients With Relapsed/Refractory B-Cell Malignancies

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CONCLUSIONS

- Sonrotoclax was well tolerated at all tested doses up to 640 mg in patients with R/R CLL/SLL and NHL
  - No cases of TLS were observed
  - Rates of discontinuation due to TEAEs were low
- Sonrotoclax demonstrated deep responses in patients with R/R CLL/SLL, with an ORR of 72.4% and a best blood uMRD4 rate of 41.4%
- Responses were observed in patients with R/R NHL, with an ORR of 20.0% and three patients achieving a CR
- Sonrotoclax is being evaluated as monotherapy in patients with R/R CLL/SLL in the BGB-11417-202 study and in combination with an anti-CD20 antibody in patients with R/R CLL in the CELESTIAL-RRCLL study

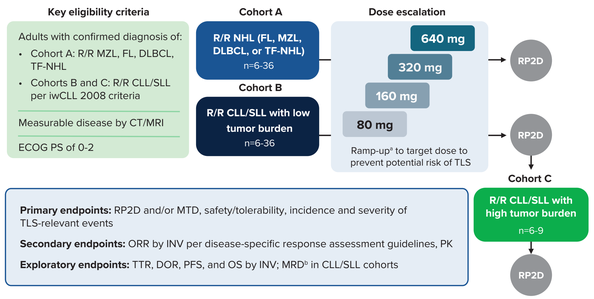
INTRODUCTION

- B-cell lymphoma 2 (BCL2) is frequently overexpressed in hematologic malignancies, which can lead to resistance to apoptosis[1]
- The first-generation BCL2 inhibitor venetoclax is an effective treatment for patients with B-cell malignancies; however, its clinical use can be limited by toxicity[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]
- Here, the safety and antitumor activity of sonrotoclax monotherapy in patients with relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and R/R non-Hodgkin lymphoma (NHL) in the BGB-11417-102 study are presented

METHODS

- BGB-11417-102 (NCT04883957) is an open-label, phase 1 study of sonrotoclax monotherapy in patients with B-cell malignancies in China (**Figure 1**)
- Sonrotoclax was administered orally once daily, with ramp-up to the target dose to prevent potential risk of tumor lysis syndrome (TLS)

Figure 1. BGB-11417-102 Study Design



[a]Dose-limiting toxicities were assessed during dose ramp-up through day 21 at the target dose. [b]MRD was assessed in peripheral blood by flow cytometry every 24 weeks; undetectable MRD was defined as <1 CLL cell per 10^4 leukocytes.

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CT, computed tomography; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; INV, investigator; iwCLL, International Workshop on CLL; MRD, measurable residual disease; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; TF, transformed; TLS, tumor lysis syndrome; TTR, time to response.

RESULTS

- As of August 23, 2024, 64 patients (CLL/SLL, n=29; NHL, n=35) had received sonrotoclax, and 16 (25%) remained on study treatment
- Median follow-up was 23.4 months (range, 1.5-35.7 months)
- Overall, 15 patients with CLL/SLL and 33 with NHL discontinued study treatment, primarily due to progressive disease
- Overall, the median age was 61.0 years and the median number of prior lines of therapy was 2 (**Table 1**)

Table 1. Demographic and Baseline Characteristics

Characteristic	CLL/SLL (n=29)	NHL (n=35)	All (N=64)
Age, median (range), years	61.0 (49-84)	59.0 (31-74)	61.0 (31-84)
Male sex, n (%)	20 (69.0)	15 (42.9)	35 (54.7)
ECOG PS			
0	11 (37.9)	12 (34.3)	23 (35.9)
1	12 (41.4)	19 (54.3)	31 (48.4)
2	6 (20.7)	4 (11.4)	10 (15.6)
Prior therapy			
No. of lines of prior therapy, median (range)	2.0 (1-7)	2.0 (1-7)	2.0 (1-7)
Prior BTK inhibitor, n (%)	15 (51.7)	13 (37.1)	28 (43.8)
Prior BTK inhibitor duration, median (range), months	6.2 (2.4-52.6)	4.5 (0.03-21.4)	4.8 (0.03-52.6)
Disease type, n (%)			
CLL	22 (75.9)	0	22 (34.4)
SLL	7 (24.1)	0	7 (10.9)
DLBCL	0	21 (60.0)	21 (32.8)
FL	0	7 (20.0)	7 (10.9)
MZL	0	4 (11.4)	4 (6.3)
Transformed B-cell NHL	0	3 (8.6)	3 (4.7)
Bulky disease, n (%)[a]	6 (20.7)	11 (31.4)	17 (26.6)
CLL/SLL risk characteristics at study entry, n/N (%)			
Binet stage C	7/14 (50.0)	NA	7/14 (50.0)
Unmutated IGHV	14/23 (60.9)	NA	14/23 (60.9)
del(17p)	2/28 (7.1)	NA	2/28 (7.1)
TP53 mutation	8/24 (33.3)	NA	8/24 (33.3)

[a]Any target lesion with a longest diameter of ≥5 cm.

Abbreviations: BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IGHV, immunoglobulin heavy-chain variable region; MZL, marginal zone lymphoma; NA, not assessed; NHL, non-Hodgkin lymphoma; SLL, small lymphocytic lymphoma.

Safety

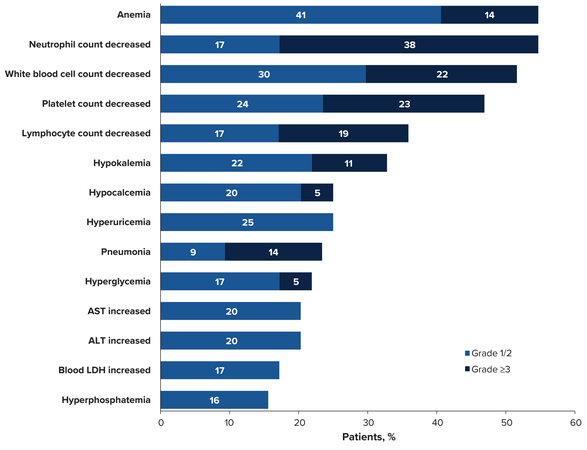
- Overall, 98.4% of patients experienced a treatment-emergent adverse event (TEAE) of any grade, and 62.5% experienced a grade ≥3 TEAE (**Table 2**)
  - The most common all-grade TEAEs were anemia and neutrophil count decreased (54.7% each)
  - The most common grade ≥3 TEAE was neutrophil count decreased (38%) (**Figure 2**)
- TEAEs led to treatment discontinuation in three patients (4.7%)
  - CLL: one patient (640 mg) with pneumonia and one patient (160 mg) with nutritional condition abnormal (decreased appetite, fatigue, and vomiting led to significant weight loss)
  - NHL: one patient (640 mg) with pneumonia
- TEAEs led to death in four patients (6.3%)
  - CLL: one patient (640 mg) with pneumonia (related to treatment); one patient (320 mg; related to disease under study) with anemia, platelet count decreased (both related to treatment), and COVID-19 pneumonia (not related to treatment); and one patient (160 mg) with multiple organ failure and hemophagocytic syndrome (both related to treatment)
  - NHL: one patient (640 mg) with pneumonia (not related to treatment)
- No laboratory or clinical TLS was reported
- The maximum tolerated dose was not reached up to 640 mg, and the recommended phase 2 dose was 320 mg once daily

Table 2. TEAE Summary

Patients, n (%)	CLL/SLL (n=29)	NHL (n=35)	All (N=64)
Any TEAE	29 (100)	34 (97.1)	63 (98.4)
Grade ≥3	21 (72.4)	19 (54.3)	40 (62.5)
Serious	16 (55.2)	6 (17.1)	22 (34.4)
Leading to dose interruption	15 (51.7)	5 (14.3)	20 (31.3)
Leading to dose reduction	2 (6.9)	1 (2.9)	3 (4.7)
Leading to treatment discontinuation	2 (6.9)	1 (2.9)	3 (4.7)
Leading to death	3 (10.3)	1 (2.9)	4 (6.3)

Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; NHL, non-Hodgkin lymphoma; TEAE, treatment-emergent adverse event.

Figure 2. TEAEs in ≥15% of Patients

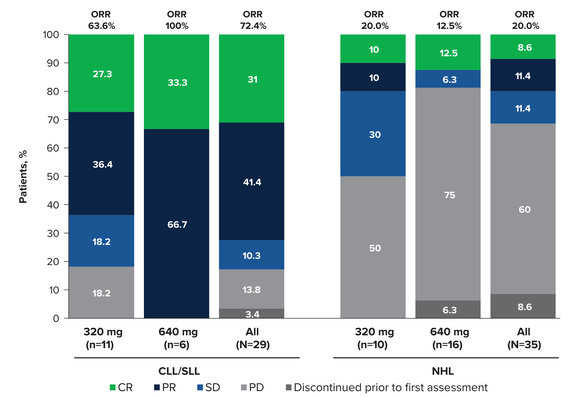


Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TEAE, treatment-emergent adverse event..

Antitumor Activity

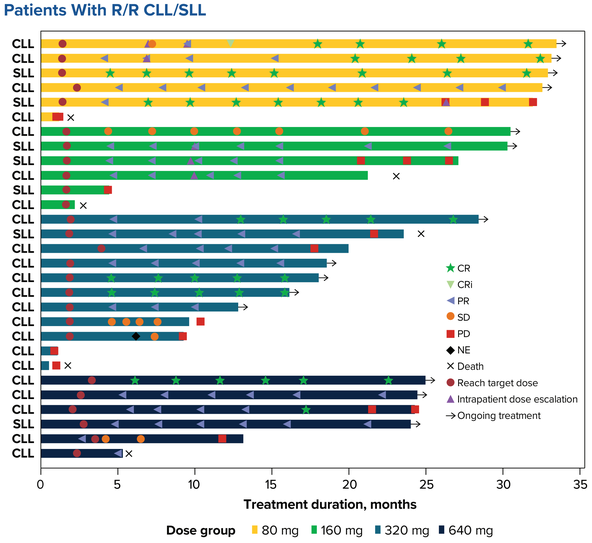
- In 29 evaluable patients with CLL/SLL and 35 with NHL, overall response rates (ORRs) across dose levels were 72.4% and 20.0%, respectively, and complete response (CR) rates were 31.0% and 8.6% (**Figure 3**)
- Median duration of response was 22.2 months in patients with CLL/SLL and 21.9 months in patients with NHL (**Figure 4**)
- In patients with CLL/SLL, the best rate of undetectable measurable residual disease (uMRD4) in blood was 41.4% (12/29) across doses, with a median time to uMRD of 7.4 months

Figure 3. Response Rates



Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 4. Treatment Duration and Investigator-Assessed Responses in Patients With R/R CLL/SLL



Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete marrow recovery; NE, not evaluable; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; SLL, small lymphocytic lymphoma.

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DISCLOSURES

ZL, ZS: Employment and may own stock: BeOne Medicines Ltd. **RV:** Employment: BeOne Medicines Ltd; Leadership: Carina Bio; Stock: BeOne Medicines Ltd, AbbVie, Gilead. **CL, KZ, JW, HH, PL, HZ, QC, SY, YD, DW:** Nothing to disclose.

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