Updated Safety and Efficacy Results of a Phase 1 Study of the Novel BCL2 Inhibitor Sonrotoclax (BGB-11417) for Relapsed/Refractory Waldenström Macroglobulinemia

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CONCLUSIONS

- Sonrotoclax monotherapy was well tolerated in patients with R/R WM and has durable antitumor activity in heavily pretreated patients
  - The highest dose tested was 640 mg; MTD was not reached
  - No TLS or atrial/ventricular arrhythmia was reported
  - Major response rate was 60.9% across dose levels and 80.0% for sonrotoclax 320 mg
  - Median PFS has not yet been reached after a median follow-up of 19.7 months
- Based on the findings of this study, further evaluation of sonrotoclax monotherapy and in combination with zanubrutinib in patients with WM is ongoing in a potentially pivotal phase 2 study

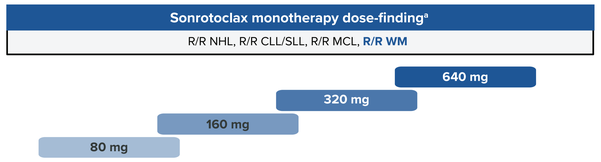
INTRODUCTION

- Waldenström macroglobulinemia (WM) is a rare, incurable, B-cell lymphoma; patients who progress on standard treatment need more tolerable and effective treatment options[1]
- Inhibition of B-cell leukemia/lymphoma 2 (BCL2) has demonstrated antitumor activity in patients with WM; however, no BCL2 inhibitors are currently approved for WM[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]
- Here, updated safety and efficacy data are presented for patients with relapsed/refractory (R/R) WM treated with sonrotoclax monotherapy in the ongoing BGB-11417-101 study

METHODS

- BGB-11417-101 (NCT04277637) is an ongoing, phase 1/1b, open-label, multicenter, dose-escalation and -expansion study of sonrotoclax as mono- or combination therapy in patients with various B-cell malignancies (**Figure 1**)
- For the R/R WM cohort, eligible patients have WM that relapsed after or was refractory to at least one prior systemic therapy and requires treatment per International Workshop on Waldenström's Macroglobulinemia-7 criteria
- Sonrotoclax monotherapy is administered orally QD, with ramp-up to the intended target dose to prevent tumor lysis syndrome (TLS), until disease progression or unacceptable toxicity
- The primary study objectives are to assess safety/tolerability, define maximum tolerable dose (MTD), and determine recommended phase 2 dose (RP2D) of sonrotoclax monotherapy; a secondary objective is to assess overall response rate (ORR), defined as minor response (MR) or better per modified Owens 2013 criteria

Figure 1. BGB-11417-101 Study Design

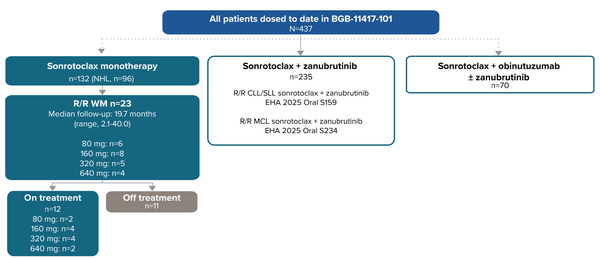


[a]The safety monitoring committee reviewed dose-level cohort data before dose escalation.
Abbreviations: CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

RESULTS

- As of March 1, 2025, a total of 23 patients with R/R WM have received sonrotoclax monotherapy and 12 (52.2%) remain on treatment (**Figure 2**)
  - Eleven patients (47.8%) discontinued treatment due to progressive disease (PD; n=7); adverse events (AEs; n=3) of multifocal neurological syndrome (not related), COVID-19 (not related), and hemolysis (related to sonrotoclax); and other reasons (n=1)

Figure 2. Patient Disposition



Data cutoff: March 1, 2025.
Abbreviations: CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

- Across cohorts, the median age was 69.0 years and the median number of prior systemic treatments was three (**Table 1**)
  - Fourteen patients (60.9%) received prior Bruton tyrosine kinase (BTK) inhibitor therapy, nine (39.1%) of whom had it as their last prior therapy

Table 1. Baseline Patient Characteristics

Characteristic	80 mg (n=6)	160 mg (n=8)	320 mg (n=5)	640 mg (n=4)	All (N=23)
Study follow-up time, median (range), months	36.3 (7.6-40.0)	25.9 (2.1-32.9)	17.0 (15.6-21.4)	9.0 (6.7-12.5)	19.7 (2.1-40)
Age, median (range), years	65.5 (48-79)	69.5 (61-87)	65.0 (61-77)	73.0 (68-84)	69.0 (48-87)
Male, n (%)	6 (100)	5 (62.5)	4 (80.0)	4 (100)	19 (82.6)
ECOG PS, n (%)					
0	3 (50.0)	2 (25.0)	1 (20.0)	2 (50.0)	8 (34.8)
1	3 (50.0)	5 (62.5)	4 (80.0)	2 (50.0)	14 (60.9)
2	0	1 (12.5)	0	0	1 (4.3)
MYD88 mutation, n/tested (%)	5/5 (100)	7/8 (87.5)	5/5 (100)	4/4 (100)	21/22 (95.4)
CXCR4 mutation, n/tested (%)	1/5 (20.0)	2/8 (25.0)	3/5 (60.0)	3/4 (75.0)	9/22 (40.9)
Prior therapy					
No. of lines of prior systemic therapy, median (range)	3.0 (1-8)	2.5 (1-9)	1.0 (1-8)	2.0 (1-3)	3.0 (1-9)
No. of prior lines of systemic therapy, n (%)					
1	1 (16.7)	3 (37.5)	3 (60.0)	2 (50.0)	9 (39.1)
2	1 (16.7)	1 (12.5)	0	0	2 (8.7)
≥3	4 (66.7)	4 (50.0)	2 (40.0)	2 (50.0)	12 (52.2)
Prior BTK inhibitor, n (%)	4 (66.7)	4 (50.0)	3 (60.0)	3 (75.0)	14 (60.9)
BTK inhibitor as last therapy, n (%)	3 (50.0)	3 (37.5)	1 (20.0)	2 (50.0)	9 (39.1)
Prior BTK inhibitor duration, median (range), months	58.0 (28.5-85.4)	53.7 (19.4-66.5)	33.1 (1.1-46.0)	37.0 (21.5-68.5)	49.5 (1.1-85.4)

Abbreviations: BTK, Bruton tyrosine kinase; *CXCR4*, C-X-C chemokine receptor type 4; ECOG PS, Eastern Cooperative Oncology Group performance status; *MYD88*, myeloid differentiation primary response 88.

- An overall summary of treatment-emergent adverse events (TEAEs) is shown in **Table 2**
  - Six patients died while on study due to PD (n=4) and AEs (n=2) of COVID-19 and pneumonia; none of these TEAEs were considered related to sonrotoclax
- Toxicity was generally the same across all tested dose levels with no new safety signals identified

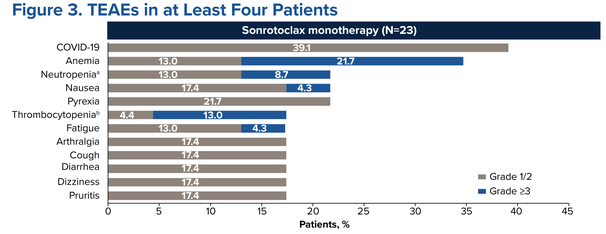
Table 2. TEAE Summary

Patients, n (%)	80 mg (n=6)	160 mg (n=8)	320 mg (n=5)	640 mg (n=4)	All (N=23)
Any TEAE	5 (83.3)	8 (100)	5 (100)	4 (100)	22 (95.7)
Grade ≥3	4 (66.7)	5 (62.5)	3 (60.0)	2 (50.0)	14 (60.9)
Serious TEAEs	3 (50.0)	5 (62.5)	2 (40.0)	1 (25.0)	11 (47.8)
Deaths	1 (16.7)[a]	1 (12.5)[b]	0	0	2 (8.7)
Led to sonrotoclax discontinuation	1 (16.7)[c]	2 (25.0)[d]	0	0	3 (13.0)
Led to sonrotoclax dose interruption	2 (33.3)	4 (50.0)	3 (60.0)	2 (50.0)	11 (47.8)
Led to sonrotoclax dose reduction	0	0	0	1 (25.0)[e]	1 (4.3)

[a]Due to pneumonia. [b]Due to COVID-19 pneumonia. [c]Due to multifocal neurological syndrome. [d]Due to COVID-19 pneumonia (n=1) and hemolysis (n=1). [e]Dose reduction was temporary.
Abbreviation: TEAE, treatment-emergent adverse event.

- The most common any-grade TEAEs across cohorts were COVID-19 (39.1%); anemia (34.8%); and neutropenia, nausea, and pyrexia (21.7% each; **Figure 3**)
  - The most common grade ≥3 TEAE was anemia (21.7%)
- No cases of laboratory or clinical TLS occurred up to the highest dose tested (640 mg)
- No cases of atrial or ventricular fibrillation were reported
- Sonrotoclax 320 mg was declared the RP2D, and no MTD was reached

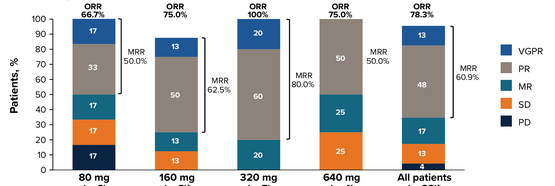
Figure 3. TEAEs in at Least Four Patients



[a]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
Abbreviation: TEAE, treatment-emergent adverse event.

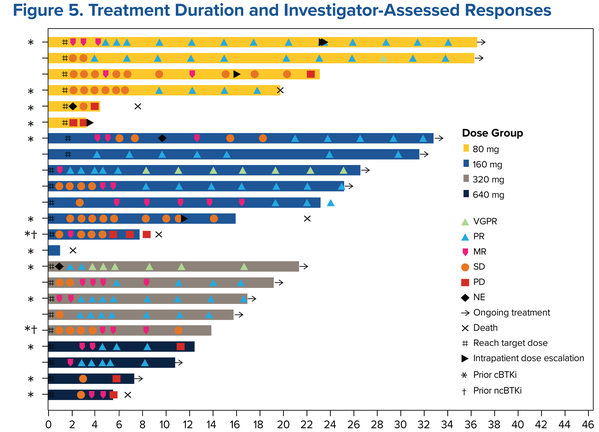
- With a median follow-up of 19.7 months, the ORR was 78.3% across all dose cohorts and 100% in the 320-mg cohort (**Figures 4 and 5**)
  - The median time to response was 4.4 months across all dose levels and 2.8 months in the 320-mg cohort
  - Major response rate (defined as partial response [PR] or better) was 60.9% across all dose cohorts and 80.0% in the 320-mg cohort
  - Among 9 patients with a BTK inhibitor as their last therapy, an ORR of 66.7% (MR, n=1; PR, n=4; very good PR [VGPR], n=1) was achieved

Figure 4. Response Rates[a]



[a]Responses were assessed per Modified Owens 2013 criteria. [b]One patient died due to a COVID-19 infection before a post-baseline response assessment. [c]For all patients as treated (N=23).
Abbreviations: MR, minor response; MRR, major response rate; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

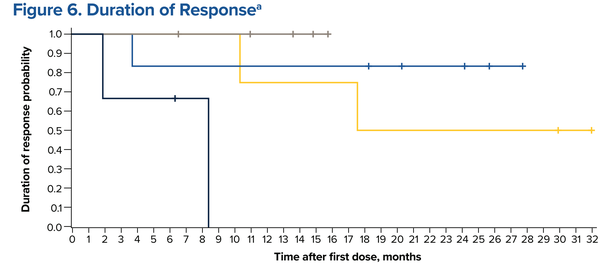
Figure 5. Treatment Duration and Investigator-Assessed Responses



Abbreviations: BTK, Bruton tyrosine kinase; cBTKi, covalent BTK inhibitor; MR, minor response; ncBTKi, noncovalent BTK inhibitor; NE, not evaluable; PD, progressive disease; PR, partial response, SD, stable disease; VGPR, very good partial response.

- With a median follow-up of 24.0 months (range, 2.1-34.0) across dose levels, median progression-free survival (PFS) was not reached (95% CI, 11.2-not evaluable [NE])
- With a median follow-up of 19.3 months, the median duration of response was not reached (95% CI, 10.3-NE; **Figure 6**)

Figure 6. Duration of Response[a]



[a]Median follow-up was estimated by reverse Kaplan-Meier method.

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DISCLOSURES

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