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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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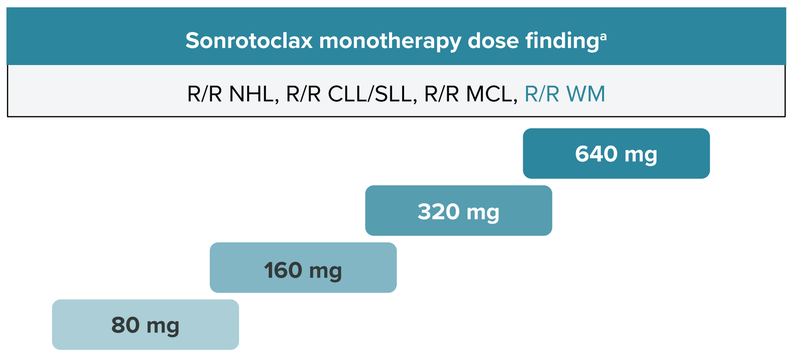
INTRODUCTION

- Waldenström macroglobulinemia (WM) is a rare, incurable, B-cell lymphoma, and more tolerable and effective treatments are needed for patients who experience progression on standard treatments[1]
- Inhibition of BCL2 has demonstrated antitumor activity in patients with WM; however, no BCL2 inhibitors are currently approved[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 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 a first-in-human, phase 1, open-label, multicenter, dose-escalation and -expansion study in patients with B-cell malignancies (**Figure 1**)
- Eligible patients had R/R WM (disease that relapsed after or was refractory to ≥1 prior systemic therapy) and required treatment per IWWM-7 criteria
- The primary objectives of the study were to assess safety/tolerability, evaluate the ramp-up dosing schedule, define the MTD, and determine the RP2D of sonrotoclax monotherapy in patients with B-cell malignancies, including R/R WM
- Responses were assessed per modified Owens 2013 criteria
- Sonrotoclax was administered orally QD with a ramp-up schedule to mitigate potential risk of TLS

Figure 1. BGB-11417-101 Study Design

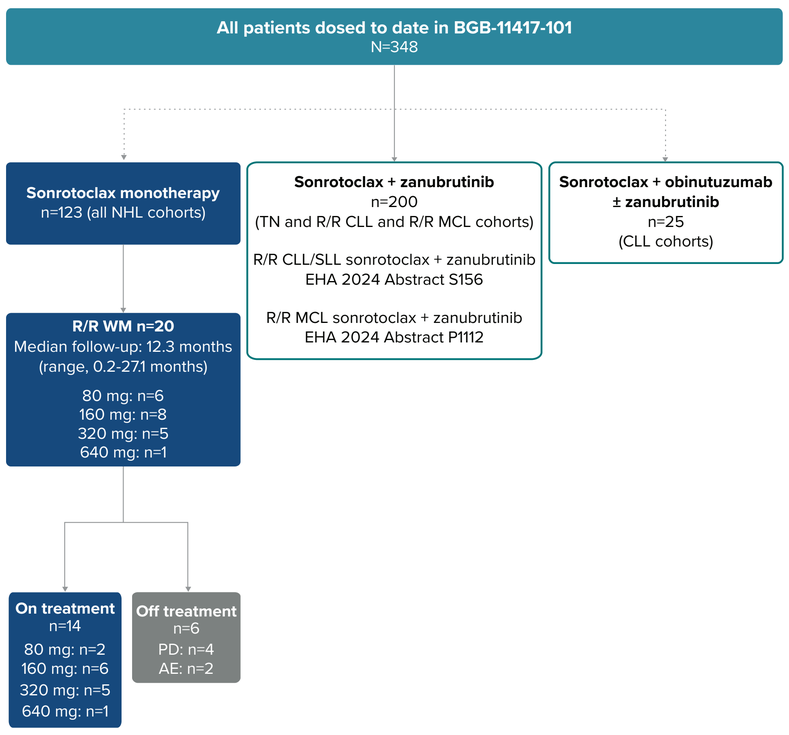


[a] The safety monitoring committee reviewed dose-level cohort data before dose escalation.

RESULTS

- As of February 4, 2024, a total of 20 patients with R/R WM had received sonrotoclax (80, 160, 320, or 640 mg), and 14 remained on treatment (**Figure 2**)
  - Six patients (30%) discontinued treatment due to progressive disease (PD; n=4) and AEs of multifocal neurological syndrome (n=1) and COVID-19 (n=1); neither AE was considered related to sonrotoclax by the investigator

Figure 2. Patient Disposition



- Across dose cohorts, the median age was 68.5 years and the median number of prior treatments was 2.5 (**Table 1**)
  - Twelve patients (60%) received prior BTK inhibitor therapy, nine (45%) 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=1)	All (N=20)
Study follow-up, median (range), months	23.4 (7.6-27.1)	13.1 (2.1-20.0)	4.1 (2.7-8.5)	0.2 (0.2-0.2)	12.3 (0.2-27.1)
Age, median (range), years	65.5 (48-79)	69.5 (61-87)	65.0 (61-77)	84.0 (84-84)	68.5 (48-87)
Male sex, n (%)	6 (100)	5 (63)	4 (80)	1 (100)	16 (80)
ECOG PS					
0	3 (50)	2 (25)	1 (20)	0	6 (30)
1	3 (50)	5 (63)	4 (80)	1 (100)	13 (65)
2	0	1 (13)	0	0	1 (5)
***MYD88* mutation, n/tested (%)**	4/4 (100)	4/4 (100)	2/2 (100)	1/1 (100)	11/11 (100)
***CXCR4* mutation, n/tested (%)**	1/4 (25)	1/4 (25)	1/2 (50)	0/1 (0)	3/11 (27)
Prior therapy					
No. of lines of prior systemic therapy, median (range)	3 (1-8)	2.5 (1-9)	1 (1-8)	3 (3-3)	2.5 (1-9)
No. of lines of prior systemic therapy, n (%)					
1	1 (17)	3 (38)	4 (80)	0	8 (40)
2	1 (17)	1 (13)	0	0	2 (10)
≥3	4 (67)	4 (50)	1 (20)	1 (100)	**10 (50)**
Prior BTK inhibitor, n (%)	4 (67)	4 (50)	3 (60)	1 (100)	**12 (60)**
BTK inhibitor as last therapy, n (%)	–	–	–	–	9 (45)
Prior BTK inhibitor duration, median (range), months	60.7 (55.3-85.4)	48.4 (19.4-54.5)	13.1 (1.1-25.1)	68.5 (68.5-68.5)	53.7 (1.1-85.4)

LDi, longest diameter; PS, performance status.

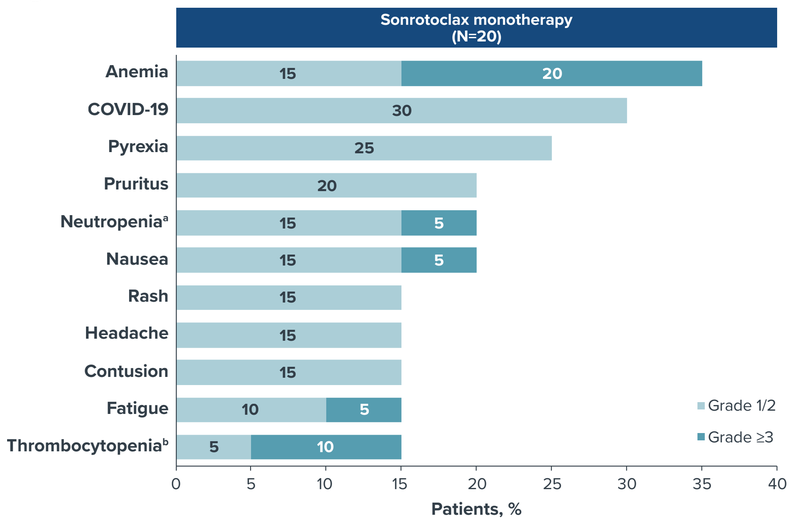
- An overall summary of TEAEs in patients with R/R WM is shown in **Table 2**
  - Four patients died while on study due to PD (n=2), COVID-19 pneumonia (n=1), and multi-organ failure (n=1); neither TEAE was related to sonrotoclax
- The most common any-grade TEAEs across cohorts were anemia (35%), COVID-19 (30%), and pyrexia (25%) (**Figure 3**)
  - The most common grade ≥3 TEAE was anemia (20%)
- No laboratory or clinical TLS was seen regardless of target dose
- One patient in the 160-mg dose group experienced a DLT of grade 3 febrile neutropenia which resolved after 2 days without dose reduction during ramp-up day 2 on 10 mg of sonrotoclax
- Dose escalation is ongoing at 640 mg, with no MTD reached at the time of data cut-off

Table 2. TEAE Summary

Patients, n (%)	80 mg (n=6)	160 mg (n=8)	320 mg (n=5)	640 mg (n=1)	All (N=20)
Any TEAE	5 (83)	8 (100)	5 (100)	0	18 (90)
Grade ≥3	3 (50)	3 (38)	1 (20)	0	7 (35)
Serious TEAEs	3 (50)	2 (25)	1 (20)	0	6 (30)
Deaths	1 (17)	1 (13)	0	0	2 (10)[a]
Led to sonrotoclax discontinuation	1 (17)	1 (13)	0	0	2 (10)[b]
Led to sonrotoclax dose interruption	2 (33)	3 (38)	0	0	5 (25)
Led to sonrotoclax dose reduction	0	0	0	0	0

[a] COVID-19 pneumonia, pneumonia. [b] COVID-19, multifocal neurological syndrome (no further information).

Figure 3. TEAEs in ≥3 Patients



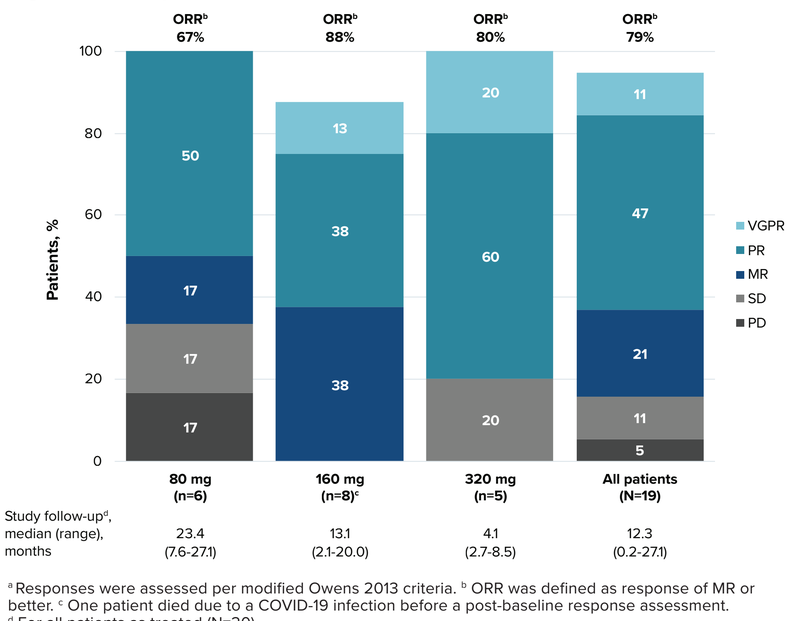
[a] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

CONCLUSIONS

- Sonrotoclax monotherapy was well tolerated in patients with R/R WM; the MTD was not reached
  - No laboratory or clinical TLS events were observed
- Preliminary antitumor activity was encouraging in this heavily pretreated population, with high and durable responses across all tested dose levels
- Further evaluation of sonrotoclax monotherapy in patients with R/R WM is ongoing in a pivotal study (BGB-11417-203)

- Response rates are shown in **Figure 4**; the 1 patient in the 640-mg cohort was not yet response evaluable

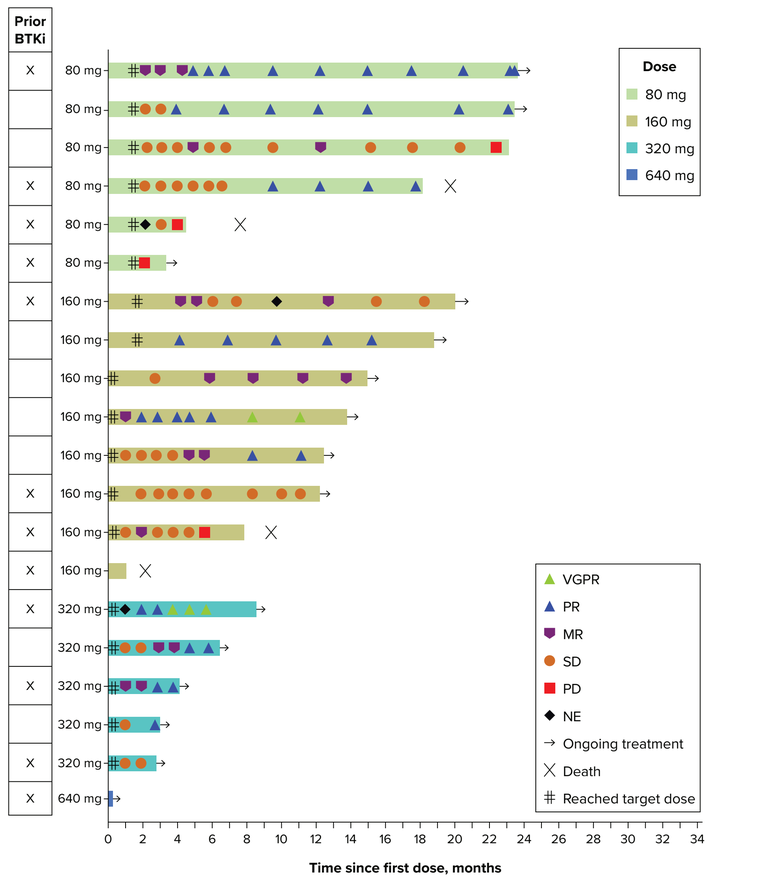
Figure 4. Response Rates[a]



Study follow-up[d], median (range), months	23.4 (7.6-27.1)	13.1 (2.1-20.0)	4.1 (2.7-8.5)	12.3 (0.2-27.1)

[a] Responses were assessed per modified Owens 2013 criteria. [b] ORR was defined as response of MR or better. [c] One patient died due to a COVID-19 infection before a post-baseline response assessment. [d] For all patients as treated (N=20).
MR, minor response; NA, not assessable; VGPR, very good partial response.

Figure 5. Treatment Duration and Investigator-Assessed Responses



BTKi, BTK inhibitor; MR, minor response; NE, not evaluable; VGPR, very good partial response.

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2. Castillo JJ, et al. *J Clin Oncol.* 2022;40(1):63-71.
3. Hu N, et al. AACR 2020. Abstract 3077.

DISCLOSURES

CYC: Consultancy, honoraria, membership on an entity's Board of Directors or advisory committees: Roche, Janssen, MSD, Gilead, Ascentage Pharma, AstraZeneca, Lilly. **CST:** Research funding: Janssen, AbbVie, BeiGene; Honoraria: Janssen, AbbVie, BeiGene, Loxo, AstraZeneca. **RGS:** Consultancy: Janssen, BeiGene; Research funding: Gilead, Takeda; Honoraria: Janssen, Takeda, BeiGene, Incyte, Astellas, Novartis, GSK; Patents and royalties: IVS (institutional agreement); Speakers bureau: Janssen, BeiGene. **MS:** Consultancy: AbbVie, Genentech, AstraZeneca, Genmab, Janssen, BeiGene, BMS, MorphoSys/Incyte, Kite Pharma, Eli Lilly, Fate Therapeutics, Nurix, Merck; Research funding: Mustang Bio, Genentech, AbbVie, BeiGene, AstraZeneca, Genmab, Morphosys/Incyte, Vincerx; Stock options: Koi Biotherapeutics; Employment: BMS (spouse). **SL:** Consulting or advisory role: BeiGene. **CD:** Consulting or advisory role: AbbVie, Ono Pharma, BMS, Seagen; Research funding: BeiGene, BMS, Fate Therapeutics, Curis Inc, Ono Pharma. **LS:** Consultancy: Octapharma, Eli Lilly; Membership on an entity's Board of Directors or advisory committees: AbbVie, AstraZeneca, BeiGene; Speakers bureau: AbbVie, Johnson & Johnson. **YF, SP:** Employment and may own stock: BeiGene. **HG:** Employment, may own stock, travel, accommodations, or expenses and leadership role: BeiGene. **WD:** Employment, may own stock and research funding: BeiGene; Grants: Merck, AstraZeneca, DTRM pharma, Octapharma, BeiGene; Advisory board: Kite Pharma. **PB:** Honoraria: AbbVie; Membership on an entity's Board of Directors or advisory committees: MSD, Janssen.

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