Ergebnisse zu Sicherheit und Wirksamkeit einer Phase 1-Studie des neuen BCL2-Inhibitors Sonrotoclax (sonro; BGB-11417) bei rezidivierter/refraktärer (R/R) Waldenström-Makroglobulinämie (WM)

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Clemens-Martin Wendtner,[1] Chan Y. Cheah,[2-4] Constantine S. Tam,[5] Ramón García Sanz,[6] Mazyar Shadman,[7,8] Sophie Leitch,[9] Christopher D'Angelo,[10] Lydia Scarfò,[11] Yiqian Fang,[12] Sheel Patel,[13] Wei Ding,[13] Haiyi Guo,[12] Peter Browett[14]

[1]Medical Clinic III, Ludwig-Maximilians University (LMU), Munich, Germany; [2]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [3]Medical School, University of Western Australia, Crawley, WA, Australia; [4]Linear Clinical Research, Nedlands, WA, Australia; [5]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [6]Hospital Universitario de Salamanca, Salamanca, Spain; [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [8]University of Washington, Seattle, WA, USA; [9]Te Whatu Ora Health New Zealand, Waitemata, Auckland, New Zealand; [10]University of Nebraska Medical Center, Omaha, NE, USA; [11]Università Vita Salute and IRCCS Ospedale San Raffaele, Milano, Italy; [12]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [13]BeiGene USA, Inc, San Mateo, CA, USA; [14]Auckland City Hospital, Grafton, Auckland, New Zealand

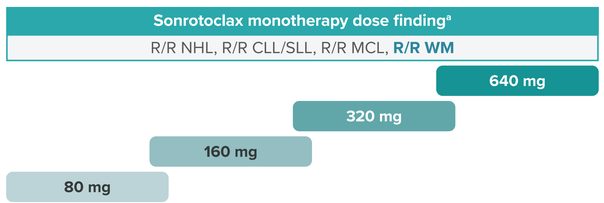
INTRODUCTION

- 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



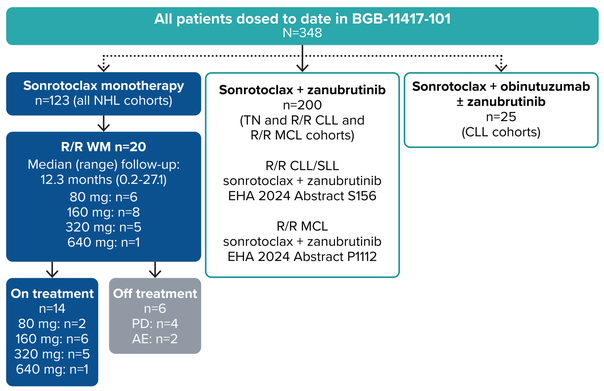
[a]The safety monitoring committee reviewed dose-level cohort data before dose escalation.

RESULTS

Disposition

- 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)

PS, performance status.

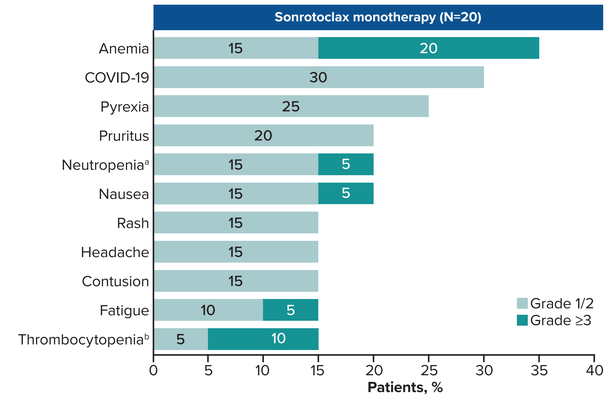
- An overall summary of TEAEs in patients with R/R WM is shown in **Table 2**
  - Four patients died while on study due to PD (n=2), COVID-19 pneumonia (n=1), and multi-organ failure (n=1); neither TEAE was related to sonrotoclax
- The most common any-grade TEAEs across cohorts were anemia (35%), COVID-19 (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).

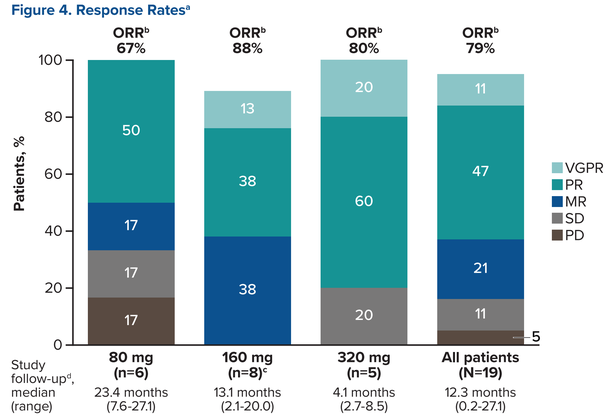
Figure 3. TEAEs in ≥3 Patients



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

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

Figure 4. Response Rates[a]

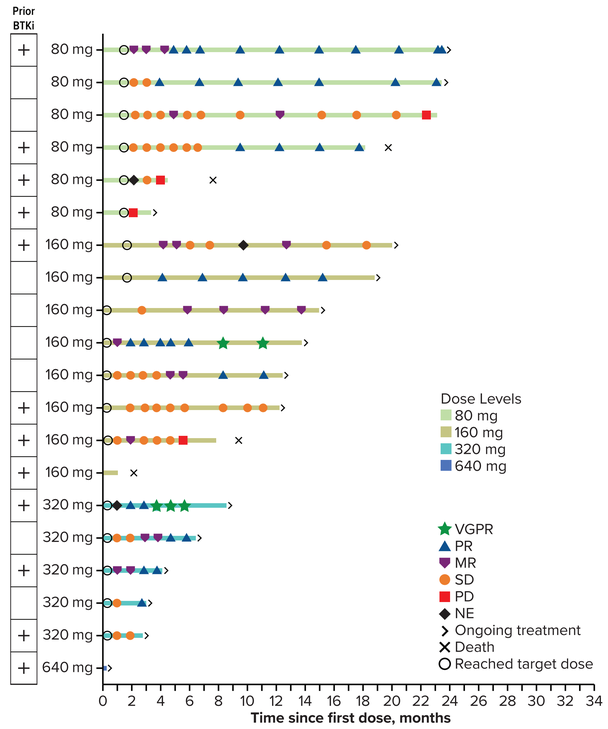


[a]Responses were assessed per modified Owens 2013 criteria. [b]ORR was defined as response of MR or better. [c]One patient died due to a COVID-19 infection before a post-baseline response assessment. [d]For all patients as treated (N=20).
MR, minor response; NA, not assessable; VGPR, very good partial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

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)

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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1. Castillo JJ, et al. *Lancet Haem.* 2020;7(11):e827-837.
2. Castillo JJ, et al. *J Clin Oncol.* 2022;40(1):63-71.
3. Hu N, et al. AACR 2020. Abstract 3077.

DISCLOSURES

CMW: Consulting or Advisory, Research funding, Travel, accommodation, expenses: BeiGene, AstraZeneca, Roche, GSK. **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); Speaker's 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; Speaker's Bureau: AbbVie, Johnson & Johnson. **YF:** Employment: BeiGene; Stock or Other Ownership: BeiGene. **SP:** Current Employment and Current equity holder in publicly traded company: BeiGene. **WD:** Research funding: BeiGene; Grants: Merck, AstraZeneca, DTRM pharma, Octapharma, BeiGene; Advisory board: Kite Pharma; Employee: BeiGene. **HG:** Current Employment and Current equity holder in publicly traded company, Travel Accommodations, Leadership: BeiGene. **PB:** Honoraria: AbbVie; Member of the board of directors or advisory committee: MSD and Janssen.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeiGene, Ltd. Medical writing was provided by Angela R. Eder, PhD, and Brittany Gifford, PharmD, of Nucleus Global, an Inizio company, and supported by BeiGene.

CORRESPONDENCE: Clemens-Martin Wendtner, clemens.wendtner@med.uni-muenchen.de

Presented at the Annual Meeting of the German, Austrian and Swiss Societies of Hematology and Medical Oncology; October 11-14, 2024; Basel, Switzerland
Data originally presented at the EHA2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain. Abstract P1110