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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Presented at the 12th International Workshop on Waldenström's Macroglobulinemia (IWWM-12); October 17-19, 2024; Prague, Czech Republic
Data originally presented at the EHA2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain. Abstract P1110

Disclosures for Ramón García-Sanz

- **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

Introduction

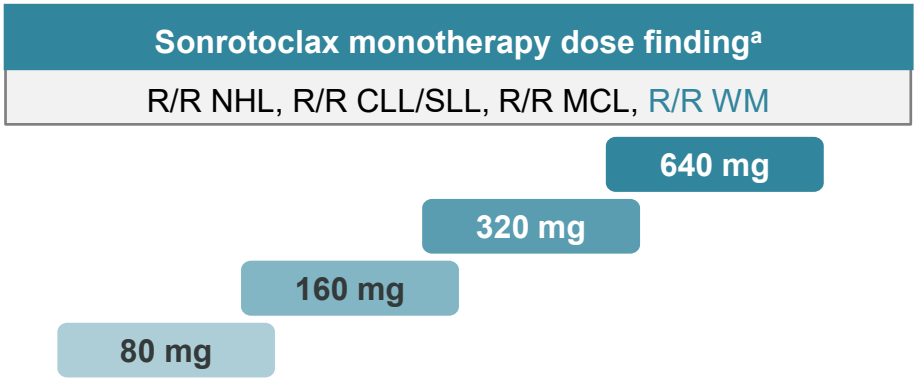
- WM is a rare, incurable, B-cell lymphoma, and more tolerable and effective treatments are needed for patients who experience progression on standard treatments[1]
- Inhibition of BCL2 has demonstrated antitumor activity in patients with WM; however, no BCL2 inhibitors are currently approved[2]
- Sonrotoclax (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 R/R WM treated with sonrotoclax monotherapy in the ongoing BGB-11417-101 study

R/R, relapsed/refractory; WM, Waldenström macroglobulinemia.

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.

BGB-11417-101 (NCT04277637) Study Design

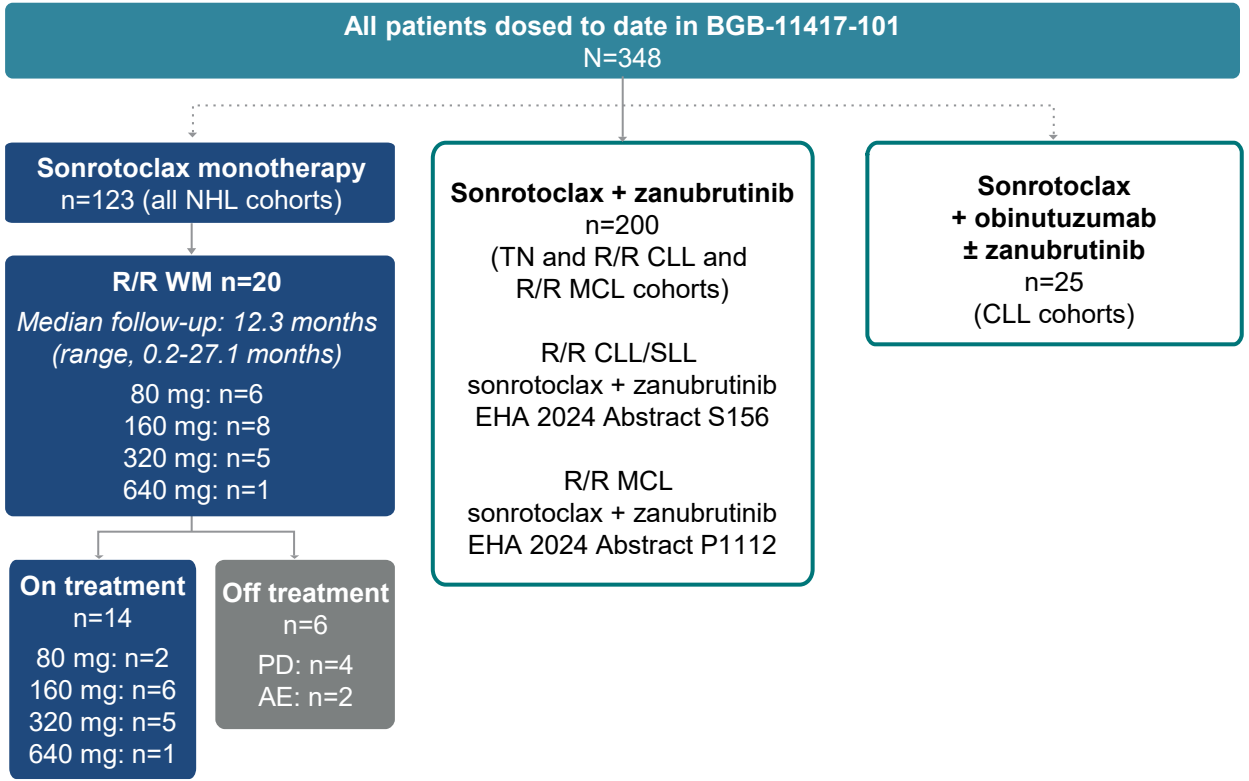
- First-in-human, phase 1, open-label, multicenter, dose-escalation and -expansion study in patients with B-cell malignancies
- Eligible patients: WM that relapsed after or was refractory to ≥1 prior systemic therapy and required treatment per IWWM-7 criteria
- Primary objectives: assess safety/tolerability, evaluate ramp-up dosing schedule, define MTD, and determine RP2D of sonrotoclax monotherapy
- Sonrotoclax was administered orally QD with a ramp-up schedule to mitigate potential risk of TLS



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

Patient Disposition

- As of February 4, 2024, 20 patients with R/R WM had received sonrotoclax (80, 160, 320, or 640 mg)
- Fourteen patients remained on treatment and 6 discontinuations (30%) occurred:
  - PD (n=4)
  - AEs not related to study drug (n=2)[a]



[a] Multifocal neurological syndrome (n=1); COVID-19 (n=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, n (%)					
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)

PS, performance status.

Baseline Patient Characteristics (cont.)

Characteristic	80 mg (n=6)	160 mg (n=8)	320 mg (n=5)	640 mg (n=1)	All (N=20)
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)

TEAE Summary

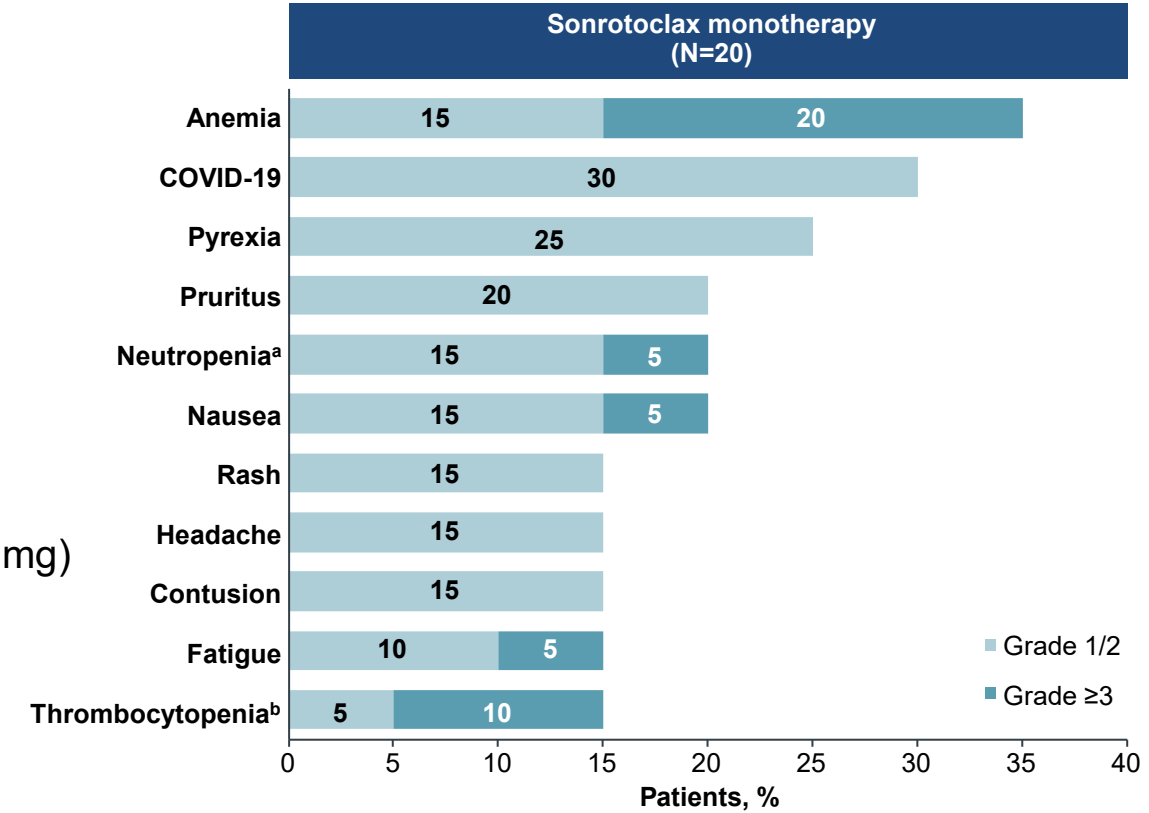
- Four deaths on study: PD (n=2), COVID-19 pneumonia (n=1), and multi-organ failure (n=1); neither TEAE was related to sonrotoclax

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)

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

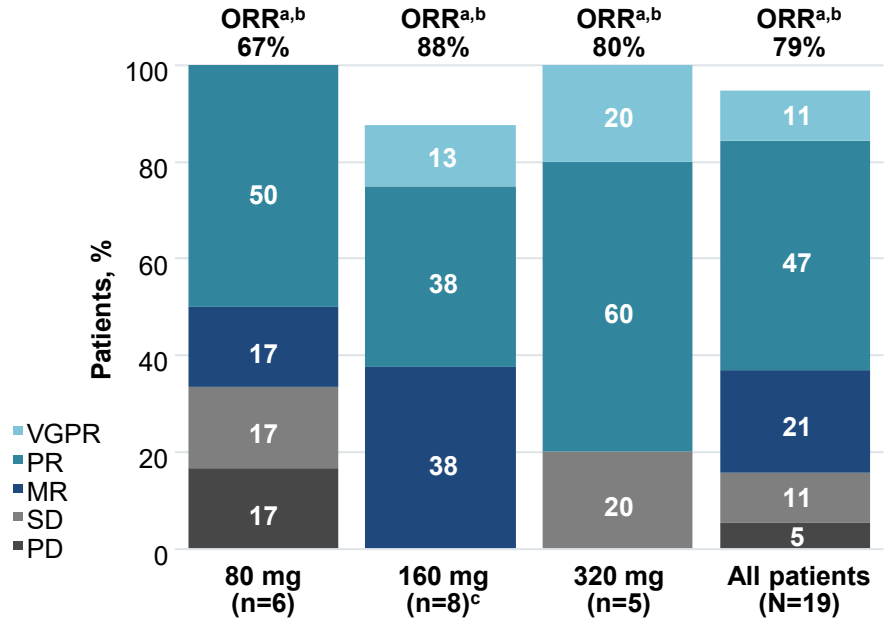
TEAEs in ≥3 Patients

- Most common any-grade TEAEs: anemia (35%), COVID-19 (30%), pyrexia (25%)
- Most common grade ≥3 TEAE: anemia (20%)
- No laboratory or clinical TLS
- One DLT (160-mg dose): grade 3 febrile neutropenia; resolved after 2 days without dose reduction during ramp-up day 2 (sonrotoclax 10 mg)
- Dose escalation ongoing at 640 mg, with no MTD reached at the time of data cut-off

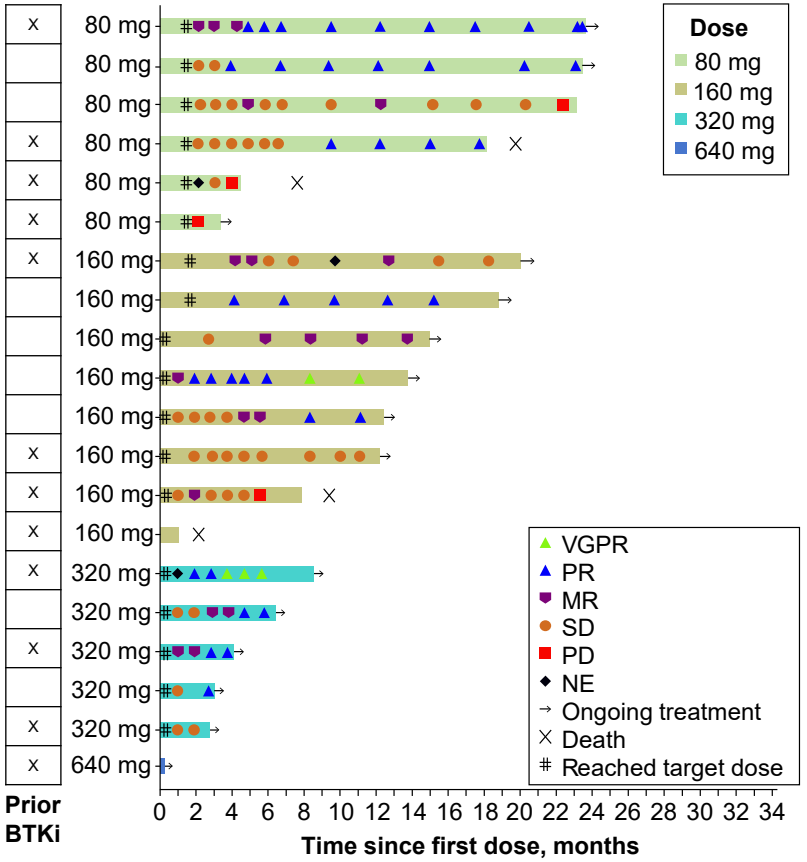


[a] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [b] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

Promising Single-Agent Antitumor Activity Across Dose Levels



[a] Responses were assessed per modified Owens 2013 criteria. [b] ORR was defined as response of MR or better.
[c] One patient (160-mg dose) died due to a COVID-19 infection before a post-baseline response assessment.
[d] For all patients as treated (N=20).
BTKi, BTK inhibitor; MR, minor response; NE, not evaluable; 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 study BGB-11417-203

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