First-Line Treatment of CLL/SLL With the All-Oral Combination of Sonrotoclax and Zanubrutinib Achieves Undetectable Minimal Residual Disease Rates of >90%, Including in Patients With del(17p)/*TP53*

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Presented at the EHA2026 Congress; June 11-14, 2026; Stockholm, Sweden
Data originally presented at the 2026 ASCO Annual Meeting; May 29-June 2; Chicago IL, USA. Abstract #7043

Disclosures for Chan Y. Cheah

- **Consultant (including expert testimony):** Dizal, BMS, Roche, Janssen, Gilead, AstraZeneca, Lilly, BeOne Medicines, Ltd, Menarini, Genmab, Sobi, CRISPR Therapeutics, Regeneron, Sanofi

Introduction

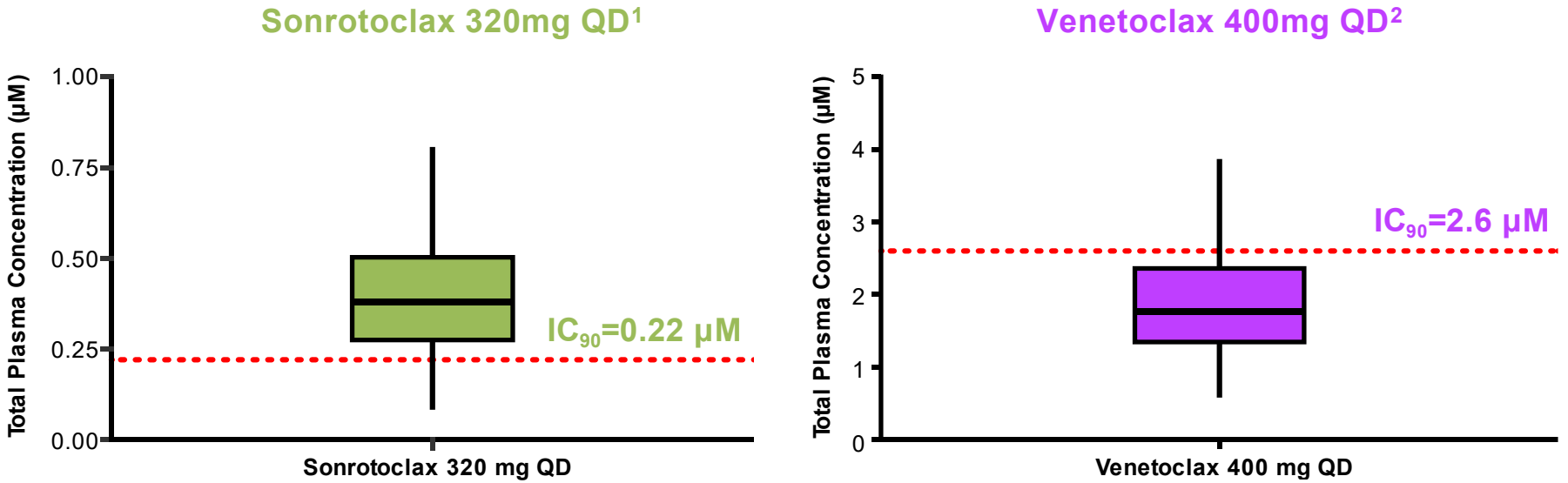
- Oral, fixed-duration BTK/BCL2 inhibitor combinations are effective and convenient first-line treatments of CLL/SLL[1]
  - Current combinations may be limited by uMRD rates and toxicities, highlighting a need for improved regimens
- Sonrotoclax, a next-generation BCL2 inhibitor, is more selective and potent than venetoclax, with an optimized pharmacokinetic profile characterized by a shorter half-life and minimal drug accumulation[2,3]
  - Sonrotoclax is approved for the treatment of R/R MCL (USA, China) and R/R CLL/SLL (China)
- Zanubrutinib is a next-generation BTK inhibitor with greater kinase selectivity and sustained BTK occupancy, and is highly effective in patients with TN and R/R CLL/SLL[4]
- Here, we report updated data from the BGB-11417-101 trial in patients with TN CLL/SLL treated with sonrotoclax plus zanubrutinib

BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; R/R, relapsed/refractory; TN, treatment-naïve; uMRD, undetectable minimal residual disease.

1. Eichhorst B, et al. *N Engl J Med.* 2023;388(19):1739-1754. 2. Guo Y, et al. *J Med Chem.* 2024;67(10):7836-7858. 3. Liu J, et al. *Blood.* 2024;143(18):1825-1836. 4. Brukinsa (zanubrutinib). Prescribing information. BeOne Medicines, Ltd; 2024.

Sonrotoclax Achieves Deep Target Inhibition at Clinical Dose

- Achieving nearly complete BCL2 inhibition (ie, IC_{90}) is key to enable deep responses such as uMRD
- Sonrotoclax has peak plasma concentrations above IC_{90} for most patients, supporting its best-in-class potential[1,2]



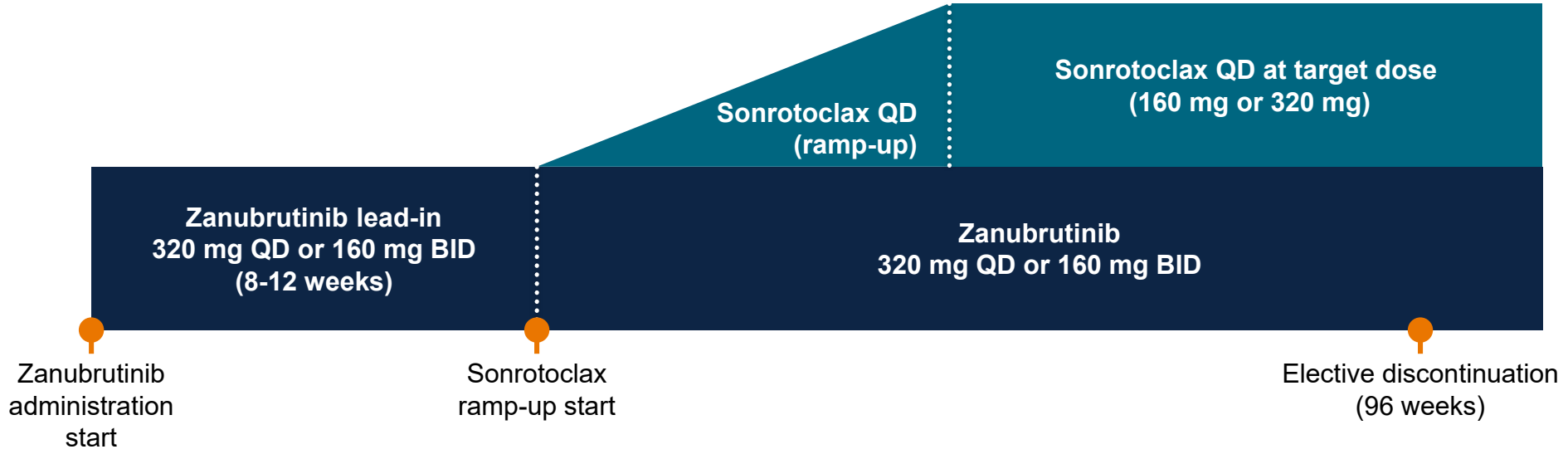
The plots shows peak plasma concentrations based on population PK simulation[1,2] relative to IC_{90} of the activity of BCL2 inhibitors to disrupt BCL2:BIM complex in human whole blood.[3] Median peak plasma concentrations are represented by the horizontal black line in the middle of each box. Lower and upper ends of the box plot represent the 25th - 75th percentile. Red dashed lines represent the IC_{90} value in plasma, using the reported IC_{90} in human whole blood corrected for blood/plasma ratio.

BCL2, B-cell lymphoma 2; PK, pharmacokinetic; QD, once daily; uMRD, undetectable minimal residual disease.

1. Sonrotoclax FDA Summary. Data on File, BeOne Medicines. 2. Jones et al. *AAPS J*. 2016;18:1192-1202; 3. Wang et al. Presented at AACR 2026.

BGB-11417-101 (NCT04277637) Study Design

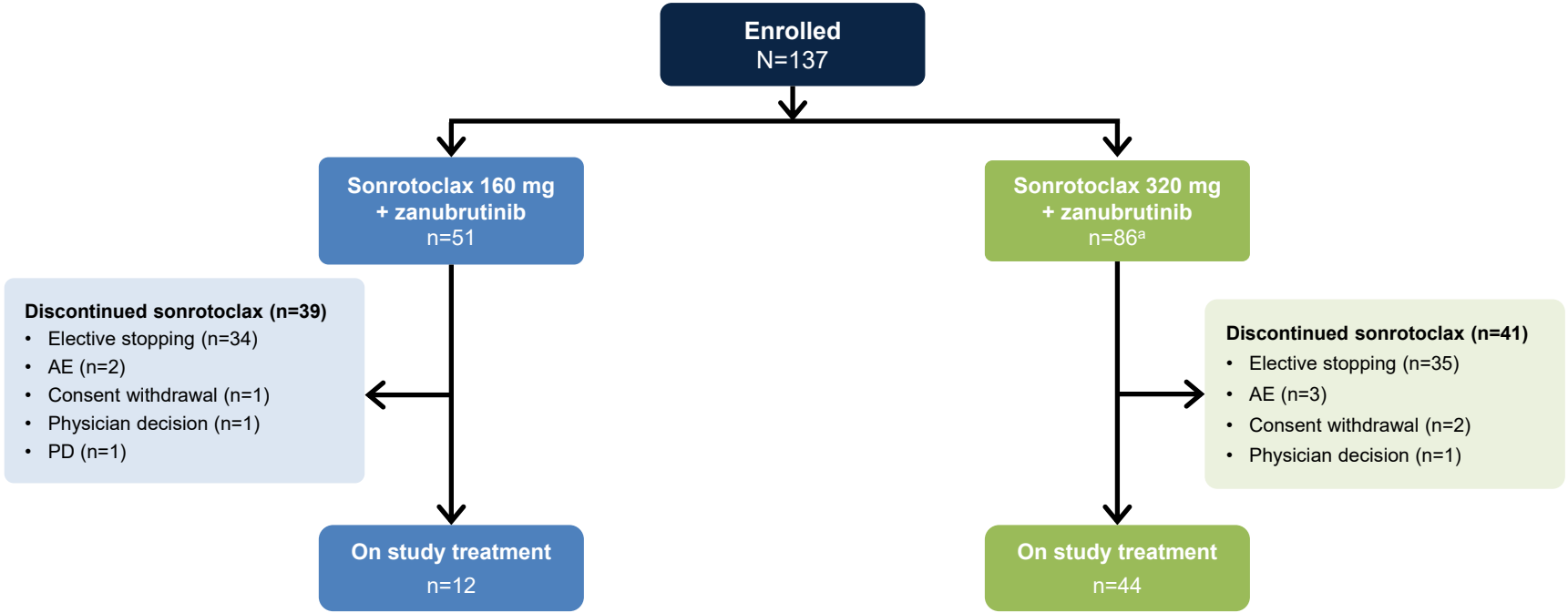
- BGB-11417-101 is a global phase 1/1b study evaluating sonrotoclax as monotherapy, or in combination with zanubrutinib and/or obinutuzumab, in patients with B-cell malignancies
- The primary objective was to determine the RP2D of sonrotoclax, and to evaluate safety and tolerability



BID, twice daily; QD, once daily; R2PD, recommended phase 2 dose.

Patient Disposition

- 137 patients with TN CLL/SLL were enrolled in sonrotoclax 160-mg (n=51) and 320-mg (n=86) cohorts
- 69 patients electively discontinued sonrotoclax after 96 weeks at target dose



[a]One patient received zanubrutinib but had not received sonrotoclax treatment.
AE, adverse event; PD, progressive disease; TN CLL/SLL, treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma.

Patient Characteristics at Baseline Were Balanced Across Cohorts

Characteristics	Sonrotoclax 160 mg + Zanubrutinib (n=51)	Sonrotoclax 320 mg + Zanubrutinib (n=86)	All Patients (N=137)
Study follow-up time, median (range), months	33.2 (17.5, 48.8)	34.1 (3.1, 45.2)	33.6 (3.1, 48.8)
Age, median (range), years	63.0 (38, 82)	61.0 (32, 84)	62.0 (32, 84)
≥65 years, n (%)	20 (39.2)	35 (40.7)	55 (40.1)
Male, n (%)	37 (72.5)	61 (70.9)	98 (71.5)
Disease type, n (%)			
CLL	48 (94.1)	82 (95.3)	130 (94.9)
SLL	3 (5.9)	4 (4.7)	7 (5.1)
Risk status, n (%)			
del(17p) or *TP53* mutation, n (%)	7 (13.7)	11 (12.8)	18 (13.1)
del(11q)	10 (19.6)	11 (12.8)	21 (15.3)
Unmutated IGHV, n (%)	34 (66.7)	48 (55.8)	82 (59.9)
High tumor burden at baseline, n (%)[a]	22 (43.1)	17 (19.8)	39 (28.5)

[a]Any lymph node ≥10 cm or lymph node ≥5 cm and absolute lymphocytes count ≥25×10^9/L
CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain variable; SLL, small lymphocytic lymphoma; sonro, sonrotoclax; zanu, zanubrutinib.

Sonrotoclax in Combination with Zanubrutinib Was Well Tolerated With Low Treatment Discontinuation Rates

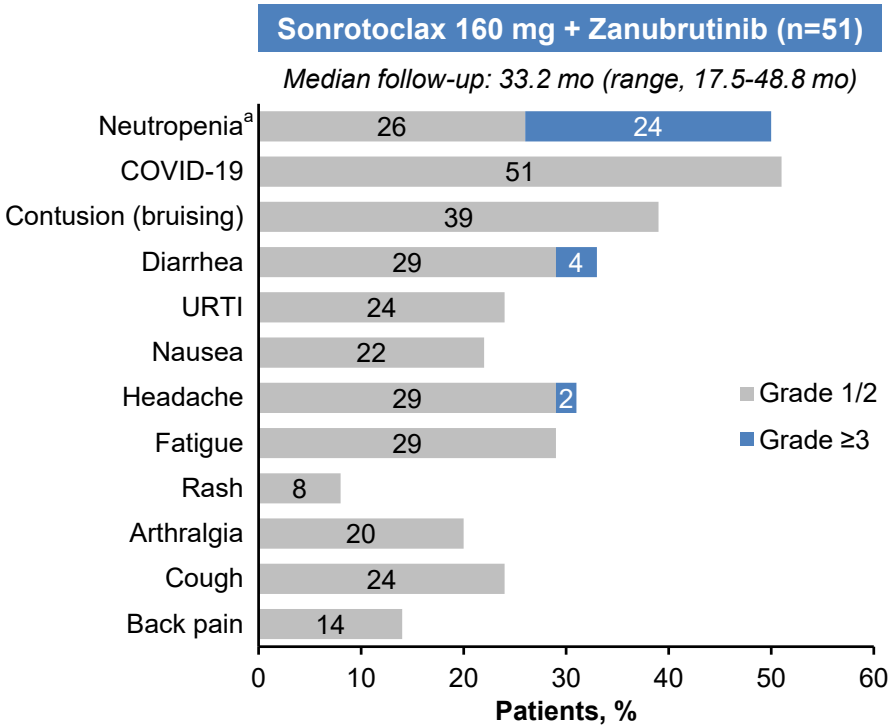
- Most TEAEs occurred at grades 1 and 2, and were transient
  - No clinical or laboratory tumor lysis syndrome occurred
  - No TEAE led to death

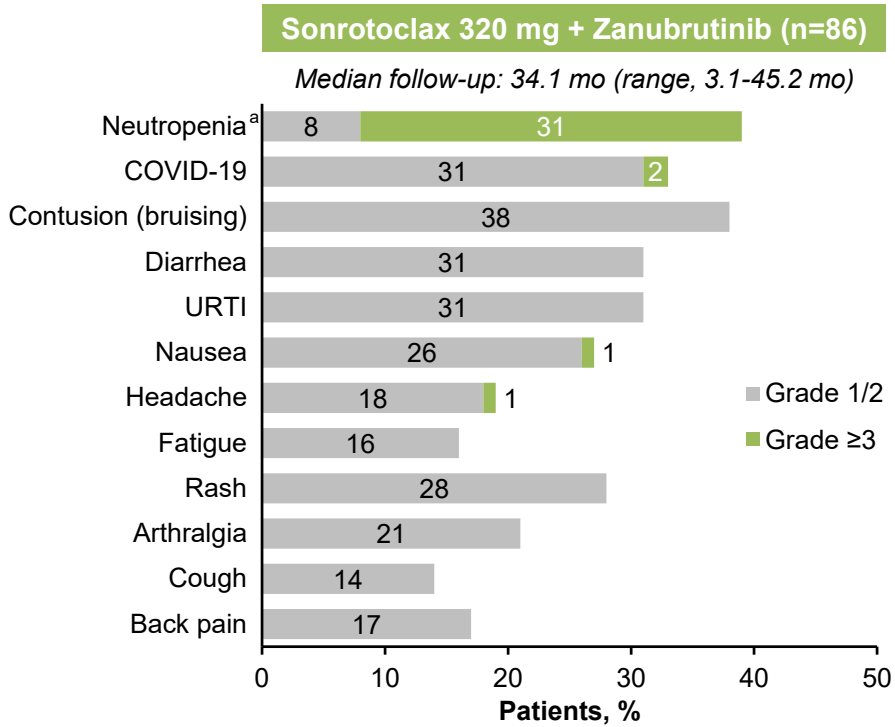
Patients, n (%)	Sonrotoclax 160 mg + Zanubrutinib (n=51)	Sonrotoclax 320 mg + Zanubrutinib (n=86)[a]	All Patients (N=137)
Any TEAEs	51 (100.0)	85 (98.8)	136 (99.3)
Grade ≥3	35 (68.6)	52 (60.5)	87 (63.5)
Serious TEAEs	20 (39.2)	27 (31.4)	47 (34.3)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of sonro	2 (3.9)	3 (3.5)	5 (3.6)
Relative dose intensity of sonro, median, %	98.9	99.0	99.0
Duration of exposure, median (range), months	29.1 (5.8,48.8)	26.2 (0.8,45.2)	26.7 (0.8,48.8)

[a]One patient received zanubrutinib but had not received sonrotoclax treatment.
sonro, sonrotoclax; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.

TEAEs Observed With Sonrotoclax + Zanubrutinib Were Mostly Low-Grade and Transient

Most Common Any-Grade TEAEs in ≥15% of Patients

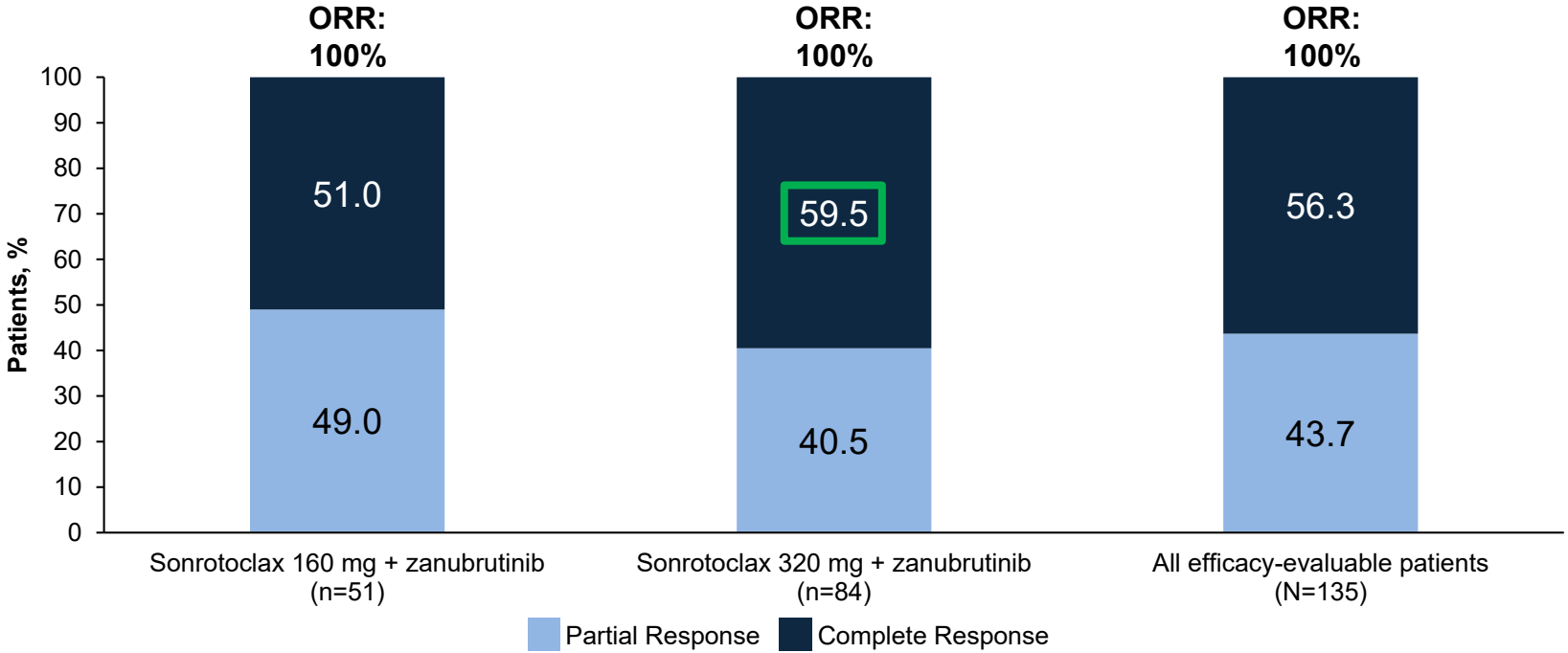




[a]Includes the combined preferred terms *neutrophil count decreased* and *neutropenia*.
mo, month; sonro, sonrotoclax; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; zanu, zanubrutinib.

Sonrotoclax + Zanubrutinib Achieved High Response Rates

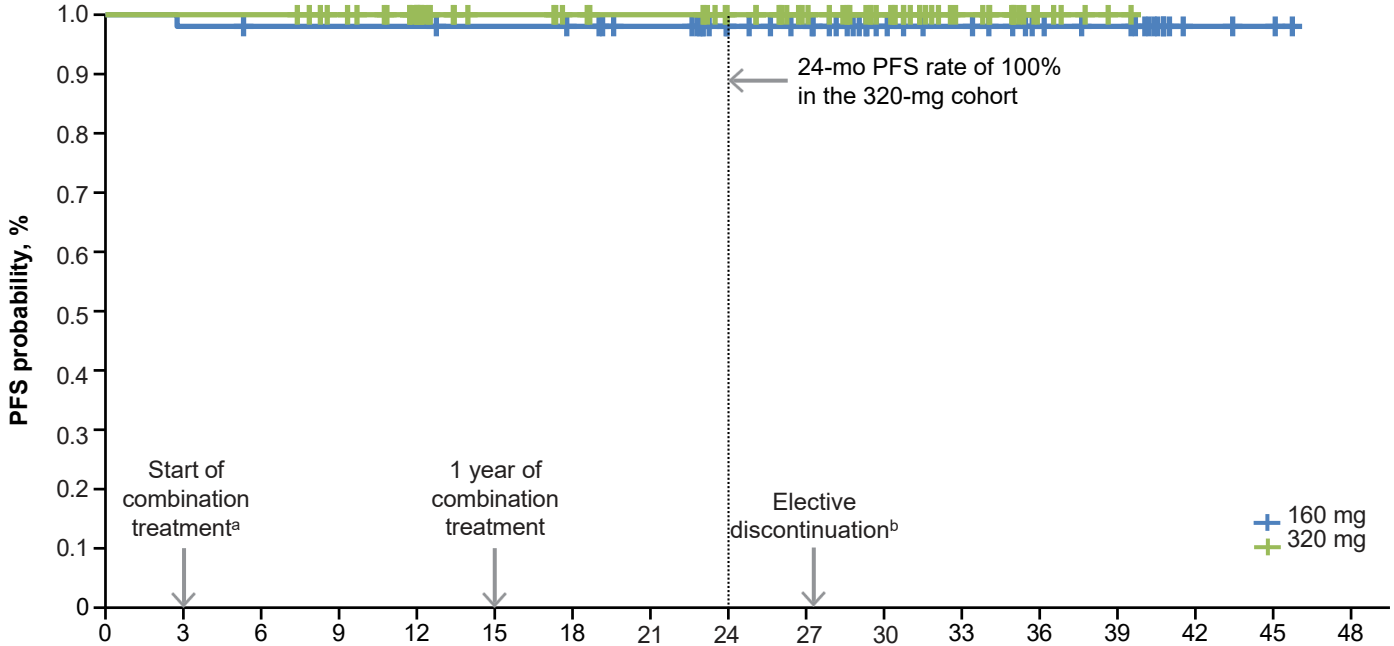
- In 135 efficacy-evaluable patients, ORR was 100%
- Median time to first response was 2.6 months (range, 1.5-10.8 months)



CR, complete response; ORR, overall response rate; PR, partial response; RP2D, recommended phase 2 dose.

Progression Free Survival: No Events Occurred in the 320-mg Cohort

- 69 patients electively discontinued sonrotoclax, the median time off treatment was 9.2 months (range, 0.6-21.6 months)



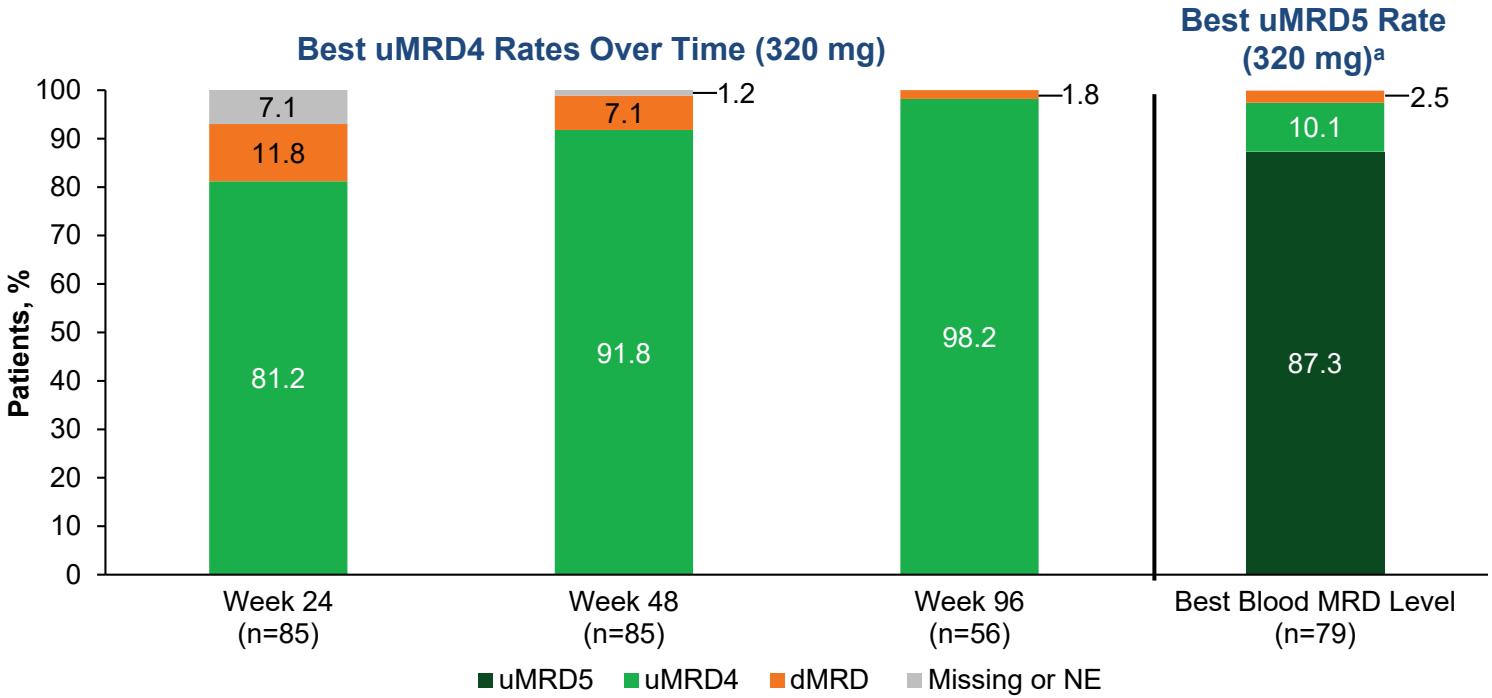
Number At Risk																	
160 mg	51	50	49	49	49	48	47	44	36	33	23	20	15	13	3	2	0
320 mg	86	84	84	80	70	59	56	54	48	40	30	16	5	1	0	0	0

In the 160-mg cohort, progressive disease was observed in one patient with Richter transformation

[a]Zanubrutinib lead-in was 8-12 weeks. [b]Protocol defined elective discontinuation after 96 weeks at target dose. mo, month; PFS, progression-free survival; RP2D, recommended phase 2 dose.

uMRD Rates Were High, Achieved Early and Increased Over Time

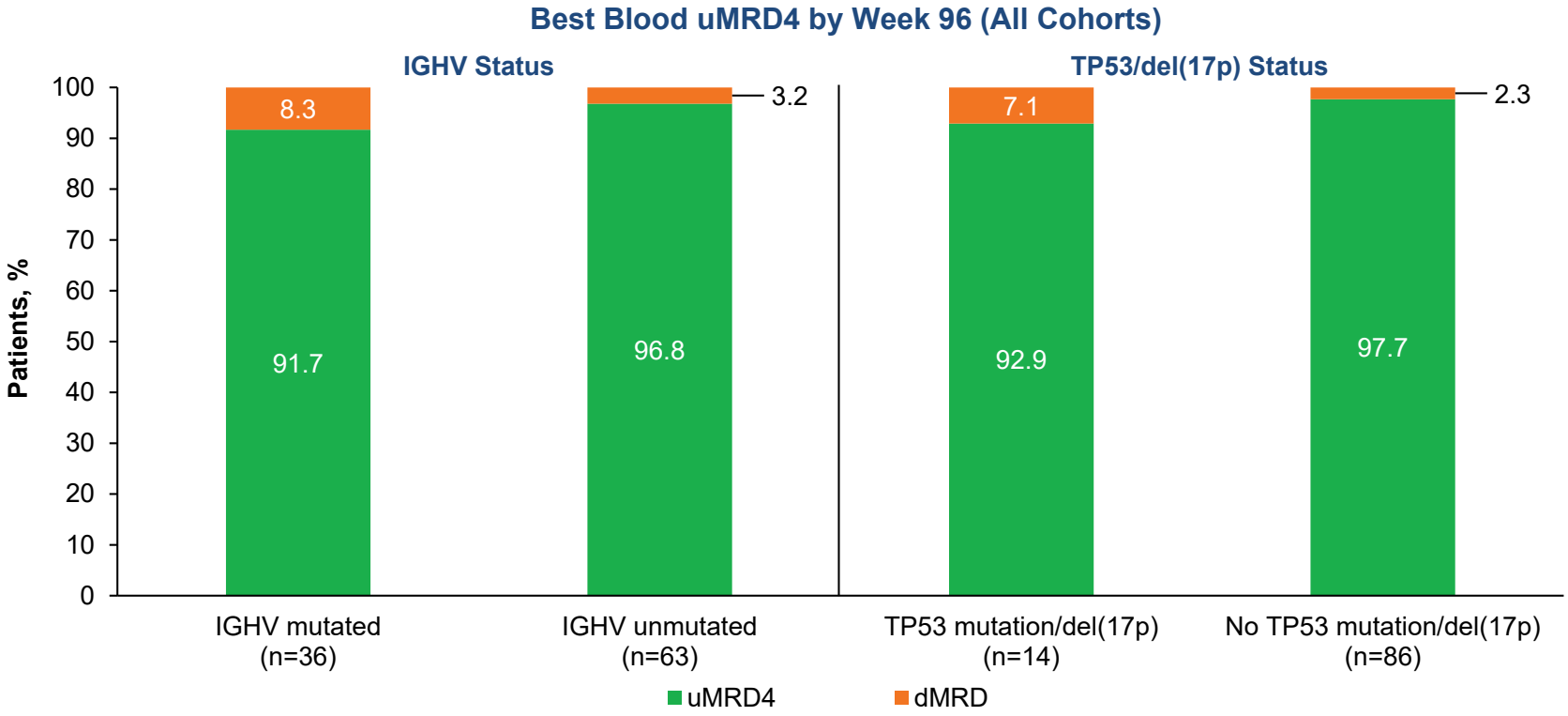
- As of the data cutoff date, no conversion from uMRD4 to dMRD occurred



Percentages are based on number of patients who should have reached each week on target dose.

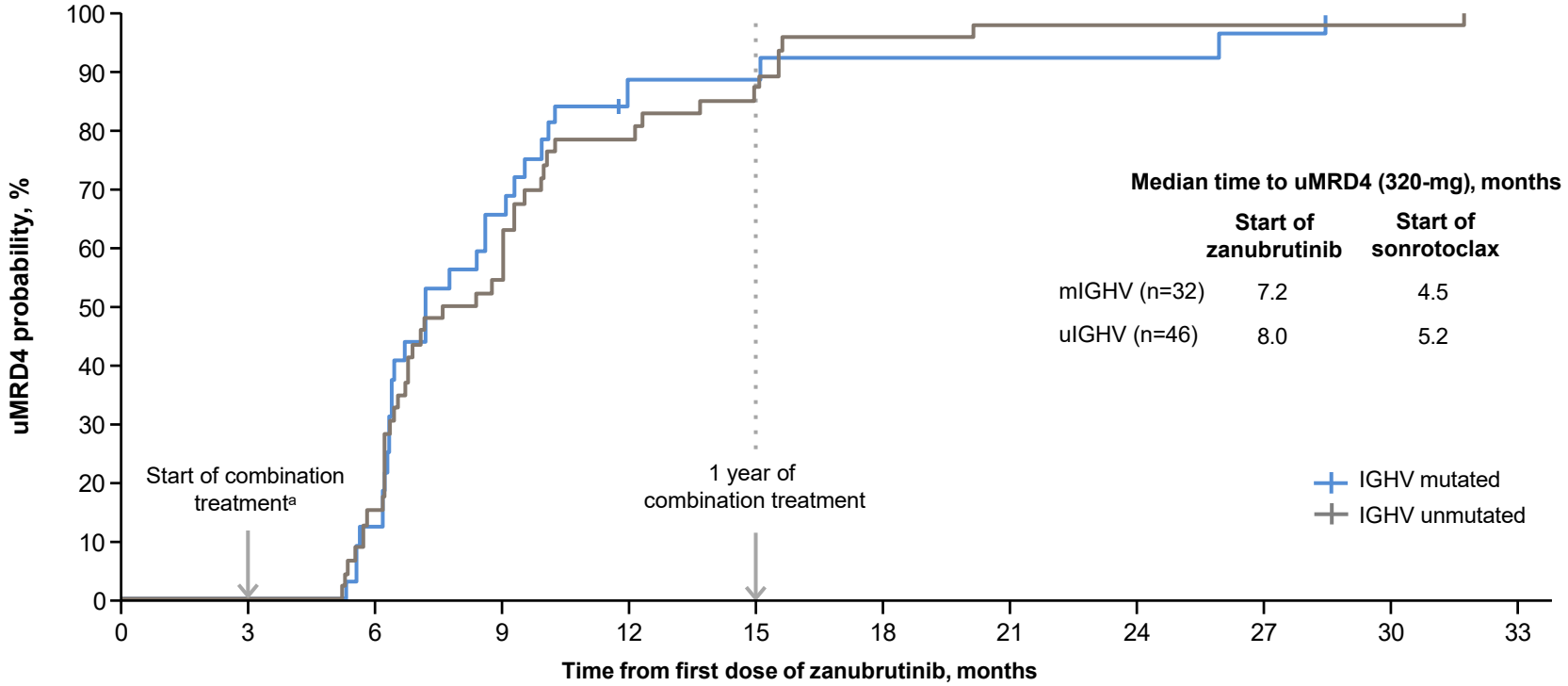
[a]Testing by Next Generation Sequencing. CLL, chronic lymphocytic leukemia; dMRD, detectable minimal residual disease; NE, not evaluable; uMRD4, undetectable minimal residual disease at <1 CLL cell per 10,000 leukocytes ($<10^4$); uMRD5, undetectable minimal residual disease at <1 CLL cell per 100,000 leukocytes ($<10^5$).

Rates of uMRD4 Were Consistent Regardless of Mutation Status



Percentages are based on number of patients who should have reached each week on target dose.
dMRD, detectable minimal residual disease; IGHV, immunoglobulin heavy chain variable; uMRD4, undetectable minimal residual disease at <1 CLL cell per 10,000 leukocytes ($<10^4$).

uMRD4 Was Achieved Rapidly, Regardless of IGHV Status



[a]Zanubrutinib lead-in was 8-12 weeks.
IGHV, immunoglobulin heavy chain variable; mIGHV, mutated IGHV; uIGHV, unmutated IGHV; uMRD4, undetectable minimal residual disease at <1 CLL cell per 10,000 leukocytes ($<10^4$).

Conclusions

- Sonrotoclax plus zanubrutinib resulted in high rates of MRD negativity in treatment-naïve CLL/SLL, with uMRD4 rates exceeding 90%, including in patients with high-risk biology
- MRD negativity was achieved after a median of ~4.5 months
- After a median study follow-up, 34.1 months, no disease progression has been observed in the 320-mg cohort
- The safety profile was favorable; no tumor lysis syndrome or treatment related deaths were reported
- Sonrotoclax (320 mg) plus zanubrutinib represents a promising treatment, with three ongoing phase 3 clinical trials in patients with treatment-naïve CLL (NCT06073821, NCT07277231) and R/R MCL (NCT06742996)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; R/R MCL, relapsed/refractory mantle cell lymphoma; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event; uMRD, undetectable minimal residual disease.

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 BeOne Medicines, Ltd
- Medical writing was supported by BeOne Medicines

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