

Ergebnisse der Phase-1 Studie des neuen BCL2-Inhibitors Sonrotoclax (sonro; BGB-11417) in Kombination mit Zanubrutinib (zanu) bei rezidivierender/refraktärer (R/R) CLL/SLL zeigen tiefes und anhaltendes Ansprechen

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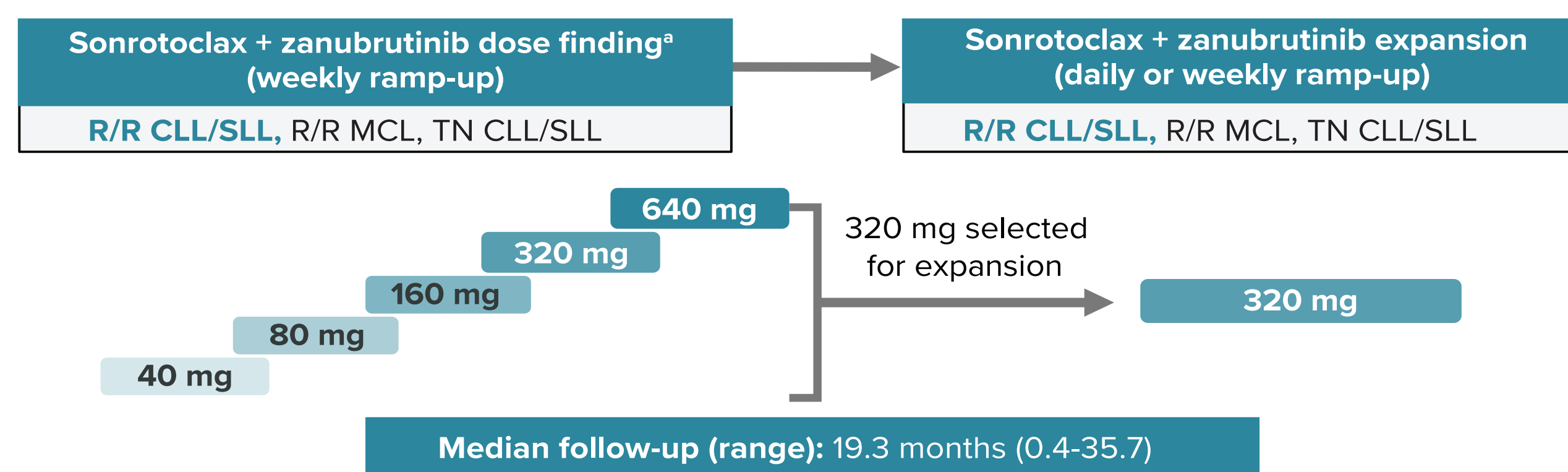
INTRODUCTION

- CLL/SLL remains incurable as many treated patients experience relapse,¹ necessitating further treatment with novel agents
- 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 accumulation²
- Zanubrutinib is a next-generation BTK inhibitor approved globally for 5 indications, including CLL^{3,4}
 - Zanubrutinib has shown superior PFS and safety/tolerability compared with ibrutinib, including fewer cardiac AEs, in patients with R/R CLL/SLL⁵
- Here, updated safety and efficacy data are presented for patients with R/R CLL/SLL treated with sonrotoclax + zanubrutinib in the ongoing BGB-11417-101 study (NCT04277637)

METHODS

- BGB-11417-101 is a global phase 1/1b study evaluating sonrotoclax as monotherapy, or in combination ± zanubrutinib, and ± obinutuzumab in patients with B-cell malignancies (Figure 1)
- The primary endpoints were safety per CTCAE v5.0, MTD, and RP2D
- Treatment consisted of 8-12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID), then in combination with sonrotoclax (with weekly or daily ramp-up to target dose) until PD

Figure 1. BGB-11417-101 Study Design



*The safety monitoring committee reviewed dose-level cohort data before dose escalation.

RESULTS

Table 1. Baseline Patient Characteristics

Characteristic	Sonro 40 mg + zanu (n=4)	Sonro 80 mg + zanu (n=9)	Sonro 160 mg + zanu (n=6)	Sonro 320 mg + zanu (n=22)	Sonro 640 mg + zanu (n=6)	All (N=47)
Study follow-up, median (range), months	34.0 (10.2-35.7)	27.7 (10.0-34.5)	29.2 (28.3-30.8)	6.8 (0.4-26.9)	18.1 (10.9-22.6)	19.3 (0.4-35.7)
Age, median (range), years	60 (50-71)	62 (55-75)	62 (41-76)	67 (36-76)	60 (53-69)	65 (36-76)
Male sex, n (%)	4 (100)	8 (89)	3 (50)	18 (82)	2 (33)	35 (75)
ECOG PS, n (%)						
0	4 (100)	5 (56)	4 (67)	11 (50)	4 (67)	28 (60)
1	0	3 (33)	2 (33)	10 (46)	2 (33)	17 (36)
Risk status, n/tested (%) ^a						
del(17p)	3/4 (75)	4/8 (50)	1/6 (17)	3/18 (17)	0	11/42 (26)
del(17p) and/or TP53 mutation	3/4 (75)	7/9 (78)	2/6 (33)	13/22 (59)	0	25/47 (53)
IGHV status, n/tested (%)						
Unmutated	1/3 (33)	6/6 (100)	3/6 (50)	3/4 (75)	0	13/19 (68)
Prior therapy						
No. of lines of prior therapy, median (range)	1.5 (1-2)	1 (1-2)	1 (1-2)	1 (1-3)	1 (1-1)	1 (1-3)
Prior BTK inhibitor, n (%) ^b	1 (25)	1 (11)	1 (17)	3 (14)	1 (17)	7 (15)
Prior BTK inhibitor duration, median (range), months	86.6 (86.6-86.6)	1.6 (1.6-1.6)	18.5 (18.5-18.5)	38.1 (34.2-49.1)	24.0 (24.0-24.0)	34.2 (1.6-86.6)

Data cutoff: February 4, 2024.
^a TP53 mutations defined as >0.1% variant allele frequency. ^b BTK inhibitor was the last prior therapy for 7 patients; all discontinued due to toxicity.

- No DLTs occurred and MTD was not reached; the 320 mg sonrotoclax + zanubrutinib cohort was expanded as RP2D
- Sonrotoclax in combination with zanubrutinib was well tolerated, with very low rates of treatment discontinuation and dose reductions; no deaths were observed (Table 2)

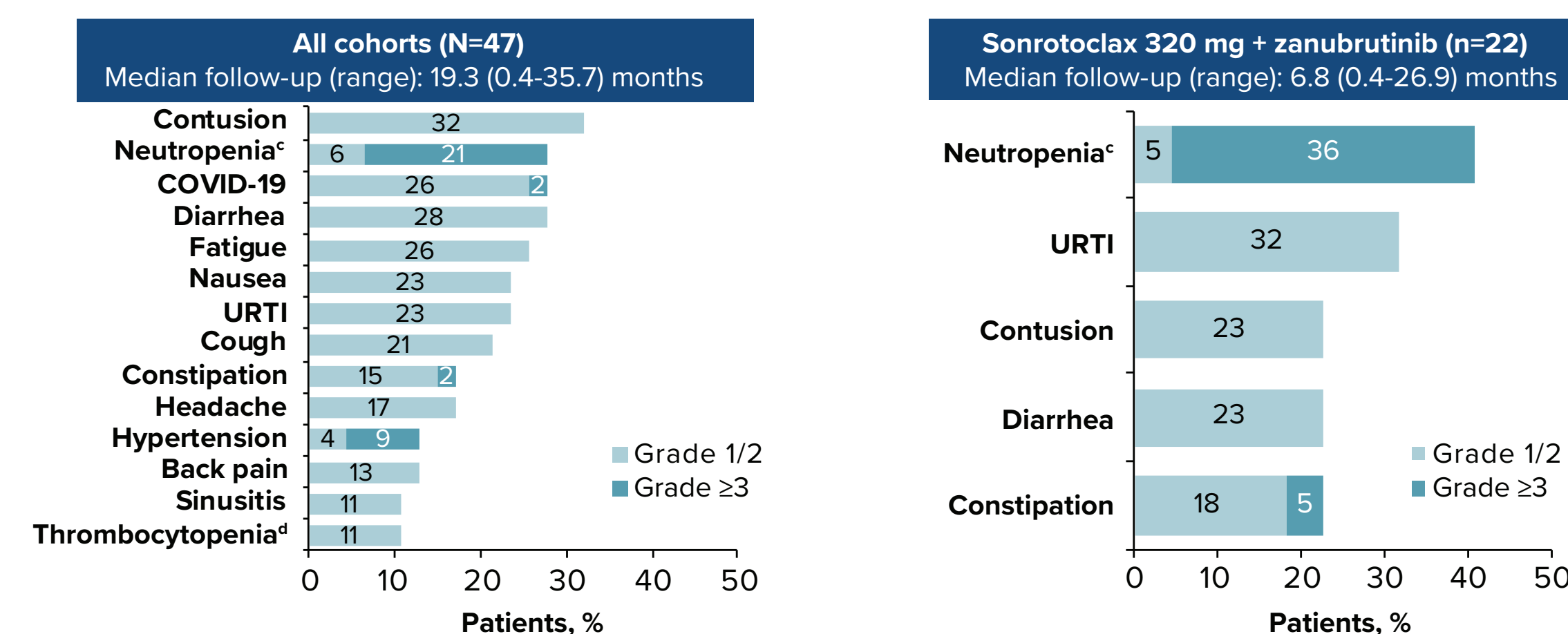
Table 2. TEAE Summary

Patients, n (%)	Sonro 40 mg + zanu (n=4)	Sonro 80 mg + zanu (n=9)	Sonro 160 mg + zanu (n=6)	Sonro 320 mg + zanu (n=22)	Sonro 640 mg + zanu (n=6)	All (N=47)
Any TEAEs	4 (100)	9 (100)	6 (100)	20 (91)	5 (83)	44 (94)
Grade ≥3	1 (25)	5 (56)	3 (50)	13 (59)	2 (33)	24 (51)
Serious TEAEs	1 (25)	1 (11)	3 (50)	7 (32)	1 (17)	13 (28)
Led to zanu discontinuation	0	1 (11) ^a	0	0	1 (17) ^c	2 (4)
Led to zanu dose reduction	0	0	0	1 (4.5) ^b	0	1 (2)
Treated with sonro, n (%)	4 (100)	9 (100)	6 (100)	19 (86) ^d	6 (100)	44 (94)
TEAEs leading to sonro discontinuation	0	0	0	0	1 (17) ^e	1 (2)
TEAEs leading to sonro dose reduction	0	0	0	0	0	0

^a 1 patient discontinued zanu due to intracranial hemorrhage. ^b 1 patient dose reduced zanu (during lead-in) due to neutropenia. ^c 1 patient discontinued both sonro and zanu due to plasma cell myeloma. ^d 3 patients are still in the zanu lead-in phase.

- TEAEs observed with sonrotoclax + zanubrutinib were mostly low grade and transient (Figure 2)
 - No cases of TLS, atrial fibrillation, or febrile neutropenia occurred
 - No patients had dose reductions due to diarrhea

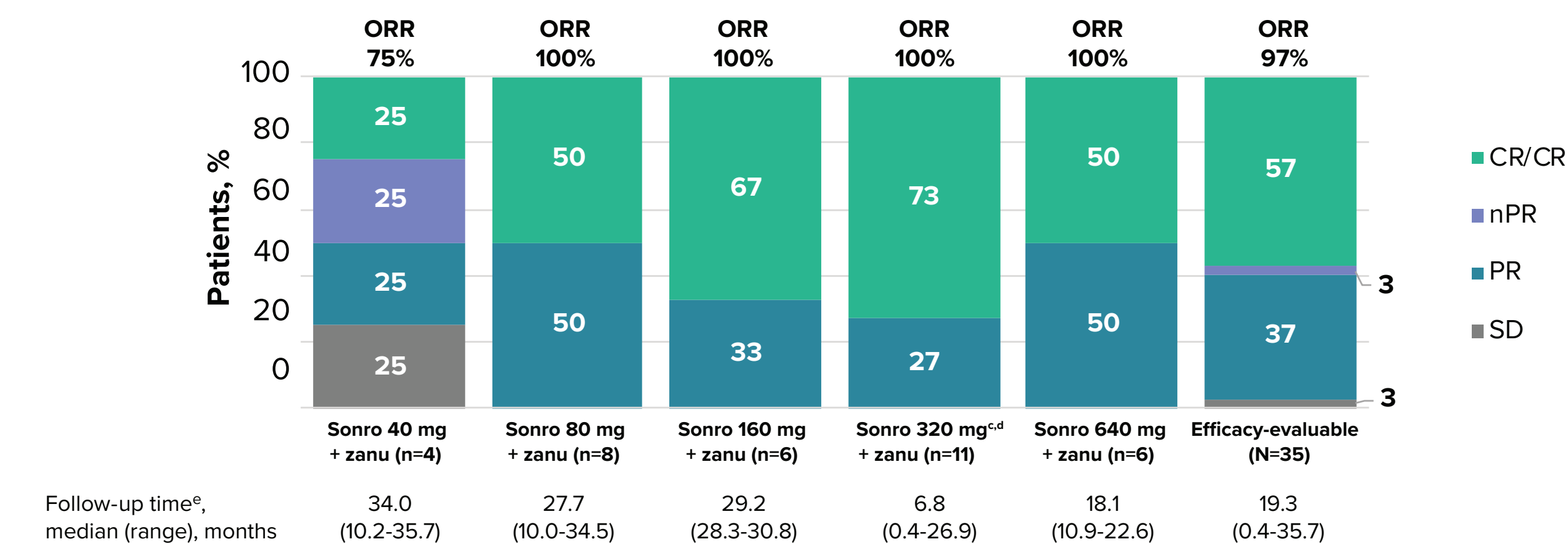
Figure 2. TEAEs in ≥5 Patients and at Sonrotoclax RP2D of 320 mg^{a,b}



^a Grade is listed as worst grade experienced by patient on any drug. ^b Hematologic AEs were graded per iwCLL criteria; nonhematologic AEs were graded per CTCAE v5.0 criteria. ^c Neutropenia combines preferred terms neutrophil count decreased and neutropenia. ^d Thrombocytopenia combines preferred terms platelet count decreased and thrombocytopenia.

- With a median study follow-up of 19.3 months, the ORR was 97%, with a 57% CR/CRi rate across all doses (Figure 3)
 - In the 320 mg cohort, the ORR was 100%, with a 73% CR/CRi rate
- The median time to CR or CRi was 9.8 months (range, 5.3-22.8 months)
- Of 6 evaluable patients with prior BTK inhibitor therapy, 4 achieved PR and 1 achieved CR

Figure 3. Overall Response Rates^{a,b}



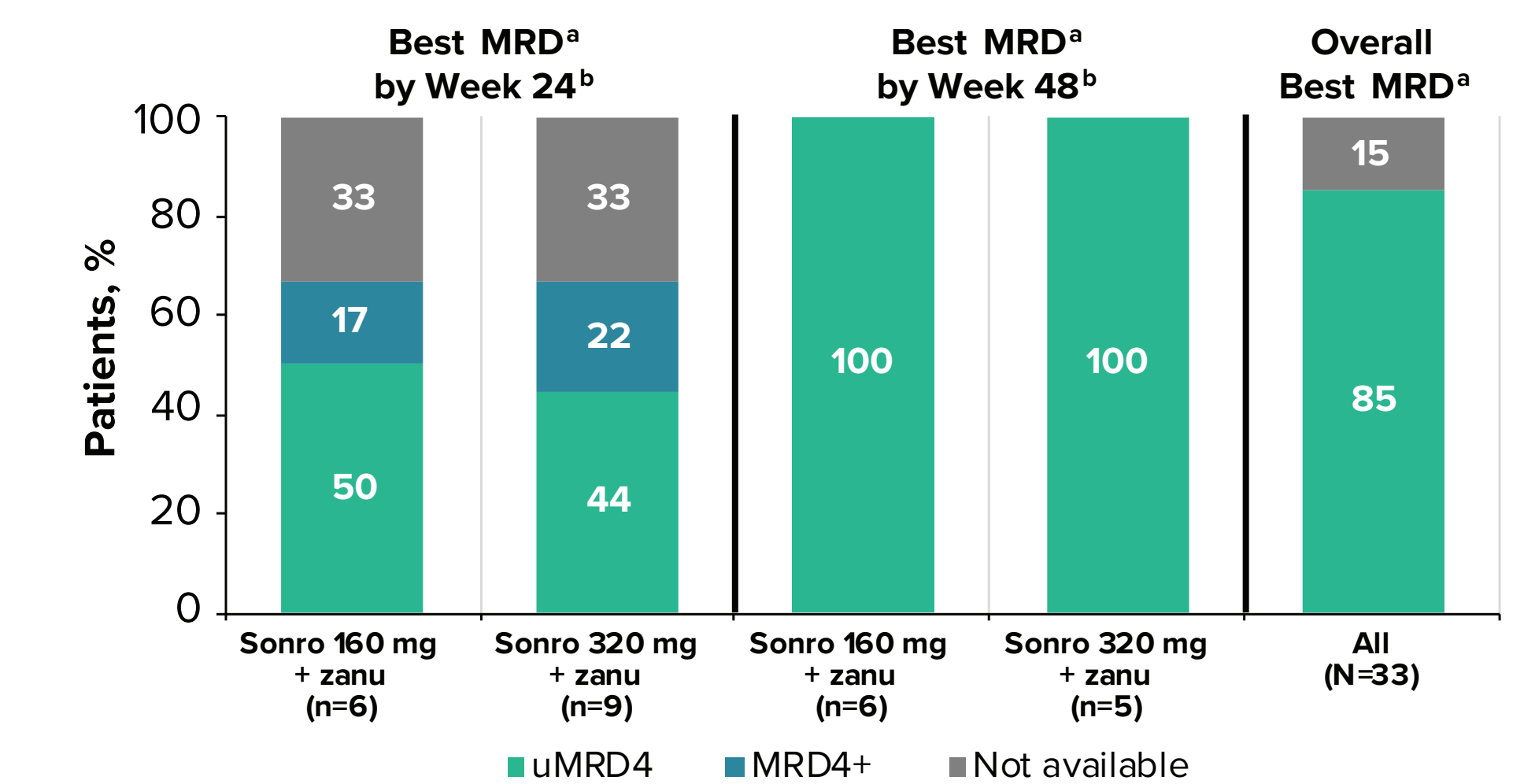
^a Responses were assessed per 2008 iwCLL criteria and percentage of response is based on number of patients who had at least 1 post-baseline tumor assessment after dosing sonro. ^b ORR was defined as PR-L or better. ^c One patient achieved CR. ^d 1 patient previously exposed to venetoclax was included and achieved CR. ^e For all patients as treated (n=47).

- Of 33 MRD-evaluable patients, 28 (85%) had uMRD at time of data cutoff (Figure 4)
- Data shows evidence of responses deepening over time
- All patients in the 160 mg, 320 mg, and 640 mg cohorts who reached week 48 achieved uMRD

CONCLUSIONS

- Sonrotoclax + zanubrutinib combination treatment had a tolerable safety profile in patients with R/R CLL/SLL at all dose levels tested up to 640 mg
 - 46/47 of patients remain on study treatment with a median follow-up of 19.3 months
 - No TLS and no cardiac toxicity, including atrial fibrillation, were observed
 - The most commonly reported hematologic TEAE was neutropenia, which was mostly transitory, with no cases of febrile neutropenia, and did not require sonrotoclax dose reductions
- Efficacy was promising in this R/R CLL/SLL population, including patients with high-risk features
 - The combination of sonrotoclax + zanubrutinib demonstrated a 97% ORR, with a CR/CRi rate of 57% across all dose levels and 100% ORR with a CR/CRi rate of 73% at 320 mg
 - Responses deepened over time with high blood MRD negativity observed by week 48 of combination therapy
 - At 19.3 months of median study follow-up, only 1 PFS event occurred in the lowest tested dose (40 mg)
- Follow up is ongoing with this promising combination therapy

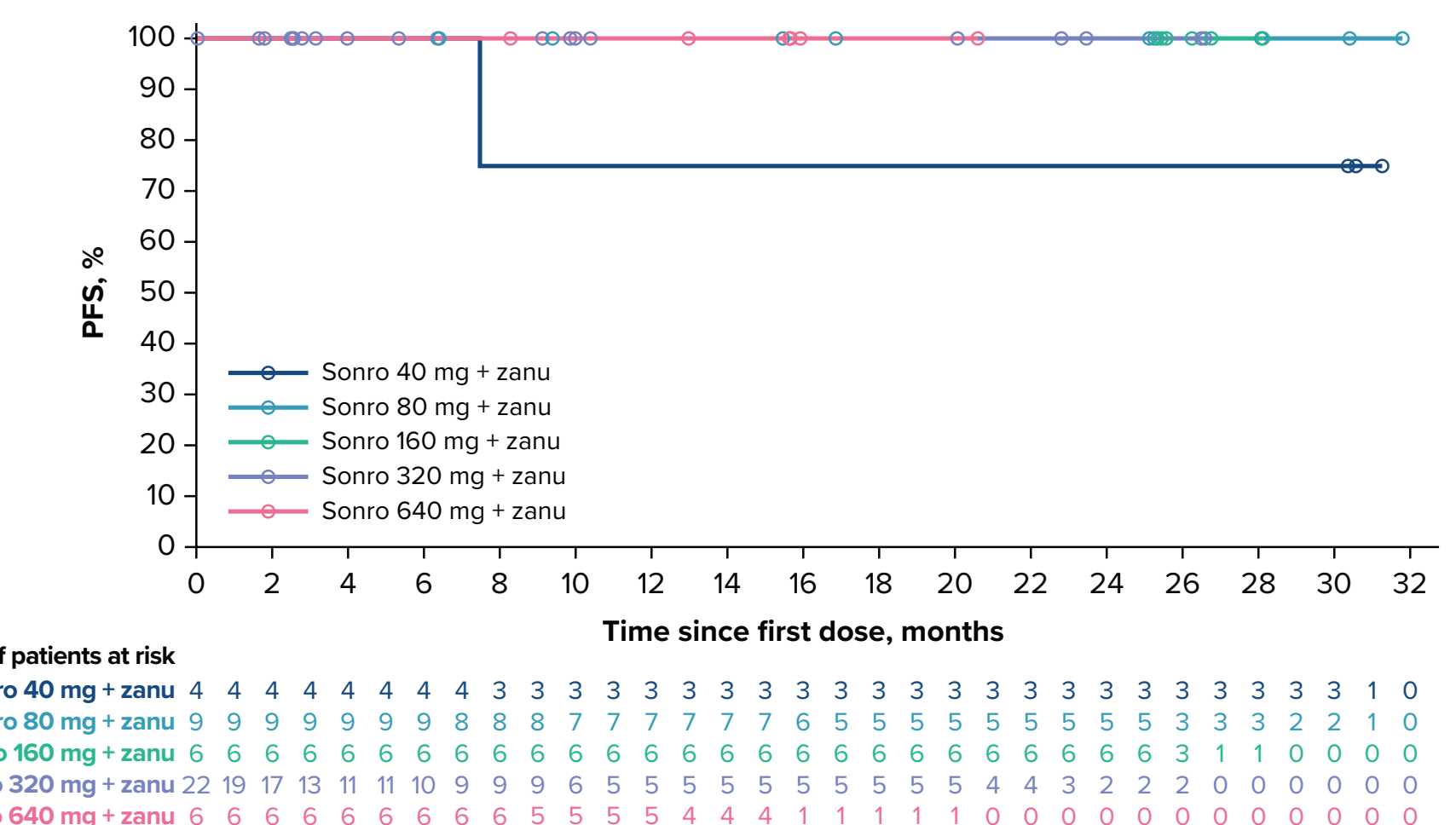
Figure 4. Best MRD in Peripheral Blood



Data cutoff: February 18, 2024.
^a Measured by an ERIC-approved flow cytometry method with 10⁻⁴ sensitivity. uMRD4 defined as <10⁻⁴ CLL cells of total WBCs. MRD4+ defined as ≥10⁻⁴ CLL cells of total WBCs. MRD is best reported within a 2-week window following the week 24/week 48 day 1 MRD assessments. ^b Week 24 or 48 of treatment at target dose, following zanu monotherapy and sonro ramp-up to target dose.

- With a median study follow-up of 19.3 months, only 1 PFS event occurred in the 40 mg cohort (Figure 5)

Figure 5. Progression-Free Survival



REFERENCES

- Hillmen P, et al. *J Clin Oncol*. 2019;37(30):2722-2729.
- Hu N, et al. *AACR 2020*. Abstract 3077.
- Brukinska. Prescribing information. BeiGene, Ltd; 2024.
- Brukinska. Summary of product characteristics. BeiGene, Ltd; 2021.
- Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

DISCLOSURES

SS: Honoraria, consulting or advisory role, research funding, speakers bureau, and travel, accommodations, or expenses; AbbVie, Amgen, AstraZeneca, BeiGene, BMS, Gilead, GSK, Hoffmann-La Roche, Janssen, Lilly, Novartis, Sunesis. SO: Consultant; AbbVie, Antengene, AstraZeneca, BeiGene, BMS, CSL Behring, Gilead, Merck, Novartis, Janssen, Roche, Takeda; Research funding; AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Janssen, Merck, Novartis, Pharmacosys, Roche, Takeda; Honoraria; AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Janssen, Merck, Novartis, Roche, Takeda; Membership on an advisory committee; AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Janssen, Merck, Novartis, Roche, Takeda; Membership on an advisory committee; research funding and/or speakers bureau; AstraZeneca, BeiGene, Lilly, Janssen; Pharmaceuticals, Juno/BMS, AbbVie, Genentech. YF, JH, SP: Employment and may own stock; BeiGene. WD: Employment and may own stock; BeiGene. Grants; Merck, AstraZeneca, DTRM Pharma, Octapharma, BeiGene; Advisory board; Kite Pharma. HG: Employment, may own stock, travel, accommodations, or expenses and leadership role; BeiGene. CST: Research funding; Janssen, AbbVie, BeiGene, Honoraria; Janssen, AbbVie, BeiGene, Loxo, AstraZeneca. AA, DW, JZH: No disclosures.

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 support was provided by Kendall Foote, PhD, of Nucleus Global, an initio company, and supported by BeiGene.