Updated Results From the Phase 1 Study of Sonrotoclax (BGB-11417), a Novel B-Cell Lymphoma 2 Inhibitor, in Combination With Zanubrutinib for Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Demonstrate Deep and Durable Responses

1514

Stephen S. Opat,[1] Constantine S. Tam,[2] Mary Ann Anderson,[3,4] Alessandra Tedeschi,[5] Emma Verner,[6,7] Masa Lasica,[8] Alejandro Arbelaez,[9] Stephan Stilgenbauer,[10] Peter Browett,[11] Sophie Leitch,[12] Eva González-Barca,[13] Mazyar Shadman,[14,15] Jing-Zhou Hou,[16] Herbert Eradat,[17] David Westerman,[18,19] Yiqian Fang,[20] James Hilger,[21] Sheel Patel,[21] Chan Y. Cheah[22-24]

[1]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [2]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [3]Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [4]The Walter and Eliza Hall Institute, Melbourne, VIC, Australia; [5]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [6]Concord Repatriation General Hospital, Concord, NSW, Australia; [7]University of Sydney, Sydney, NSW, Australia; [8]St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [9]Pindara Private Hospital, Benowa, QLD, Australia; [10]Ulm University, Ulm, Germany; [11]Auckland City Hospital, Grafton, Auckland, New Zealand; [12]Te Whatu Ora, Health New Zealand, Waitemata, Auckland, New Zealand; [13]Institut Català d'Oncologia Hospitalet, Universitat de Barcelona, IDIBELL, Barcelona, Spain; [14]Fred Hutchinson Cancer Center, Seattle, WA, USA; [15]University of Washington, Seattle, WA, USA; [16]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [17]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [18]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [19]University of Melbourne, Melbourne, VIC, Australia; [20]BeOne Medicines Ltd, Shanghai, China; [21]BeOne Medicines Ltd, San Carlos, CA, USA; [22]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [23]Medical School, University of Western Australia, Crawley, WA, Australia; [24]Linear Clinical Research, Nedlands, WA, Australia

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
  - No TLS (laboratory or clinical) was observed
  - The most commonly reported TEAE was neutropenia, which was mostly transitory, with no cases of febrile neutropenia, and did not require sonrotoclax dose reductions
- With a median follow-up of 32 months, substantial efficacy was observed in this R/R CLL/SLL population, including patients with high-risk features
  - The combination of sonrotoclax + zanubrutinib demonstrated a high response rate, including 100% ORR, with a CR/CRi rate of 48% at 320 mg
  - High and early blood uMRD4 was seen by week 24 of combination therapy, and deepened over time
  - Thirteen patients electively discontinued treatment and continue to remain in remission as of the data cutoff date
- These preliminary data highlight the potential for all-oral, time-limited therapy with sonrotoclax + zanubrutinib in patients with R/R CLL to drive meaningful disease control, regardless of del(17p) and/or *TP53* mutation status

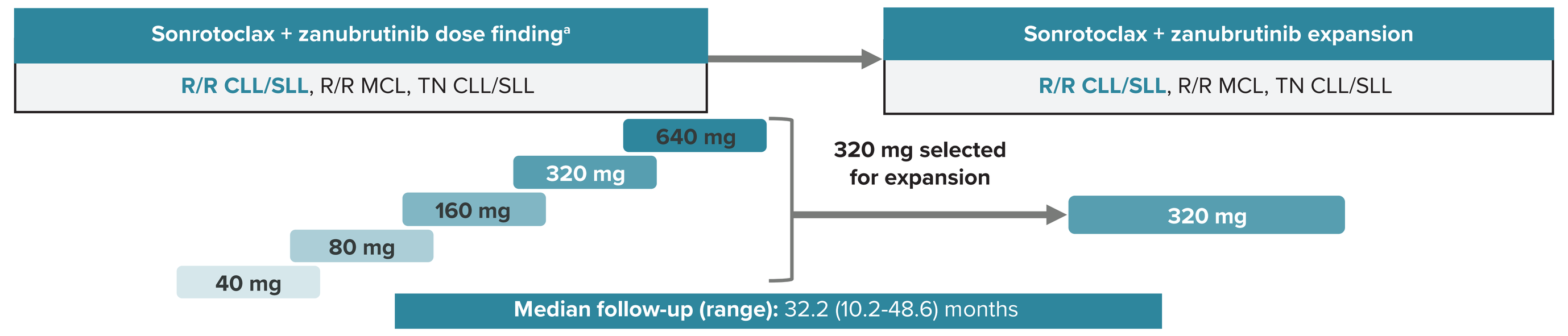
INTRODUCTION

- Most treated patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) experience disease 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 accumulation[2]
- Zanubrutinib is a highly potent and selective next-generation BTK inhibitor that was designed to provide complete and sustained target inhibition and is the only BTK inhibitor to demonstrate superiority over ibrutinib in a head-to-head phase 3 trial[3]
- Fixed-duration therapies are emerging as a new treatment option[4]; however, there are no approved BCL2 inhibitor + BTK inhibitor regimens for patients with relapsed/refractory (R/R) CLL/SLL
- Here, updated safety and efficacy data, including preliminary results from time-limited therapy, are presented for patients with R/R CLL/SLL treated with sonrotoclax + zanubrutinib in the ongoing BGB-11417-101 study

METHODS

- BGB-11417-101 is a global phase 1/1b study of sonrotoclax as monotherapy, or in combination ± zanubrutinib, and ± obinutuzumab in patients with B-cell malignancies
- For the R/R CLL/SLL cohort, treatment consists of 8-12 weeks of zanubrutinib lead-in (320 mg once daily or 160 mg twice daily), then zanubrutinib + sonrotoclax until disease progression, intolerance, or elective discontinuation (**Figure 1**)
- Patients who reach 96 weeks of combination treatment may elect to stop study drug treatment while remaining on study and following all procedures (protocol-defined elective discontinuation)
- The primary endpoints are safety per NCI-CTCAE v5.0, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D); overall response rate (ORR) per iwCLL 2018 criteria and undetectable measurable residual disease (uMRD) in blood by standardized ERIC flow cytometry assay every 24 weeks are secondary and exploratory endpoints

Figure 1. BGB-11417-101 (NCT04277637) Study Design



[a]The safety monitoring committee reviewed dose-level cohort data before dose escalation.
Abbreviations: CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; R/R, relapsed/refractory; TN, treatment naive.

RESULTS

Baseline Characteristics

- As of March 1, 2025, 47 patients with R/R CLL/SLL were enrolled and had received combination treatment (sonrotoclax doses: 40 mg, n=4; 80 mg, n=9; 160 mg, n=6; 320 mg, n=22; 640 mg, n=6)
- The median age was 65 (range, 36-76) years; 38% of tested patients (16/42) had del(17p) and/or *TP53* mutation, and 73% (30/41) had unmutated IGHV (**Table 1**)
- The median study follow-up was 32.2 months (range, 10.2-48.6 months)

Table 1. Baseline Characteristics and Demographics

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	46.8 (10.2-48.6)	40.6 (22.9-47.3)	42.0 (41.1-43.6)	19.6 (13.2-39.7)	30.9 (23.8-35.5)	32.2 (10.2-48.6)
Age, median (range), years	60.0 (50-71)	62.0 (55-75)	61.5 (41-76)	67.0 (36-76)	59.5 (53-69)	65.0 (36-76)
Male, n (%)	4 (100)	8 (89)	3 (50)	18 (82)	2 (33)	35 (74)
ECOG PS, n (%)						
0	4 (100)	5 (56)	4 (67)	11 (50)	4 (67)	28 (60)
1	0	3 (33)	2 (33)	10 (45)	2 (33)	17 (36)
Mutation status, n/N (%)						
del(17p)	3/4 (75)	4/8 (50)	1/6 (17)	3/18 (17)	0	11/42 (26)
del(17p) and/or *TP53* mutation[a]	3/4 (75)	5/8 (63)	1/6 (17)	7/19 (37)	0	16/42 (38)
Unmutated IGHV	2/4 (50)	8/9 (89)	3/6 (50)	14/17 (82)	3/5 (60)	30/41 (73)
Prior therapy						
No. of lines of prior therapy, median (range)	1.5 (1-2)	1.0 (1-2)	1.0 (1-2)	1.0 (1-3)	1.0 (1-1)	1.0 (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: March 1, 2025
[a]*TP53* mutation defined as ≥5% variant allele frequency. [b]BTK inhibitor was the last prior therapy for 7 patients; all discontinued due to toxicity.
Abbreviations: BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region; sonro, sonrotoclax; zanu, zanubrutinib.

Safety

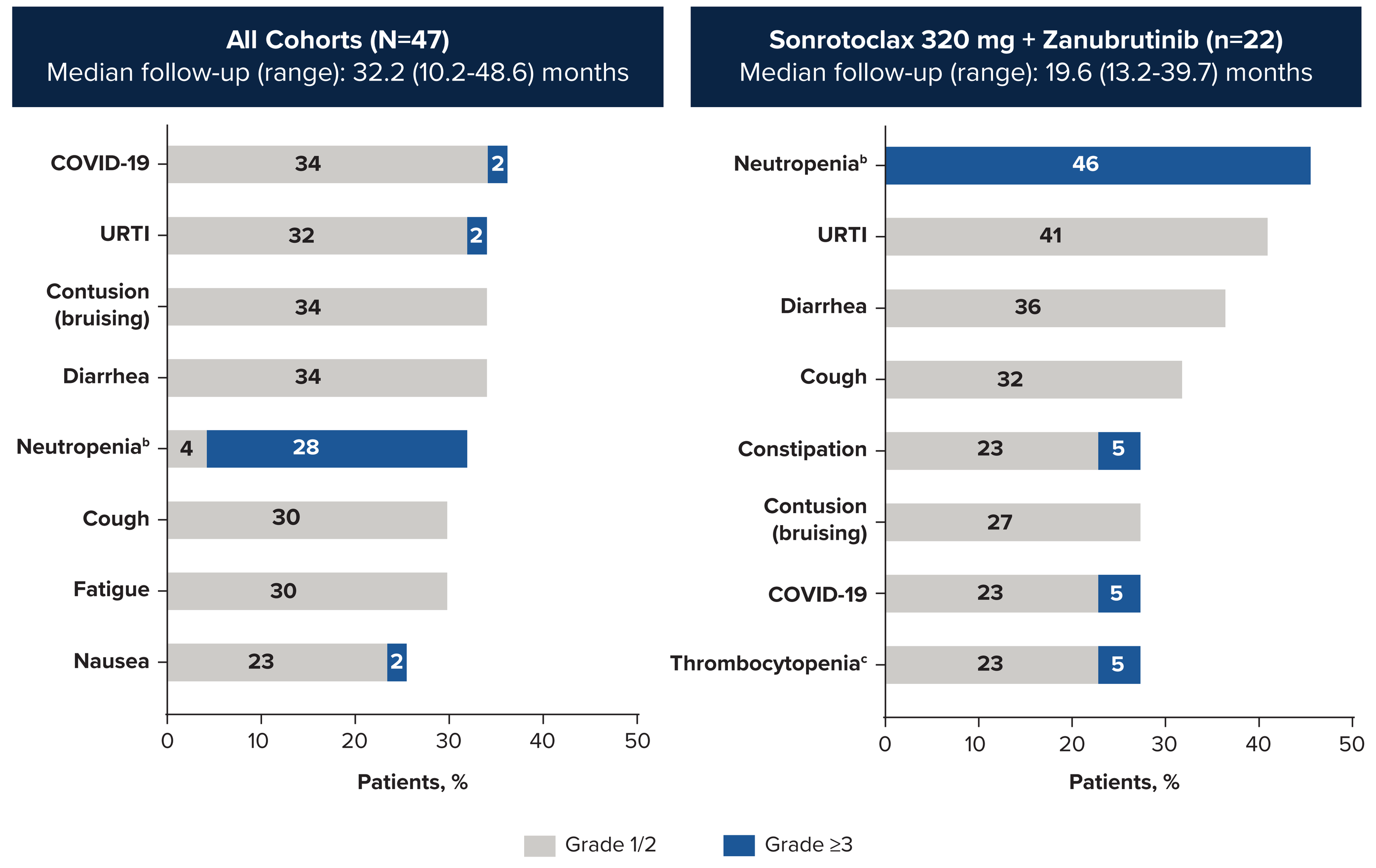
- Overall, no dose-limited toxicities occurred and MTD was not reached with doses up to 640 mg (**Table 2**); the sonrotoclax 320 mg + zanubrutinib cohort was expanded as RP2D
- The most common any-grade and grade ≥3 treatment-emergent AEs (TEAEs) were COVID-19 (36%) and neutropenia (28%), respectively (**Figure 2**)
- TEAEs led to 4 treatment discontinuations (8%) and no deaths
- No cases of tumor lysis syndrome (TLS), febrile neutropenia, or dose reductions due to diarrhea occurred

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)	22 (100)	5 (83)	46 (98)
Grade ≥3	1 (25)	7 (78)	3 (50)	18 (82)	3 (50)	32 (68)
Serious TEAEs	1 (25)	3 (33)	3 (50)	11 (50)	3 (50)	21 (45)
Led to zanu discontinuation	0	1 (11)[a]	0	2 (9)[b]	1 (17)[c]	4 (8)
Led to zanu dose reduction	0	1 (11)[d]	0	2 (9)[e]	1 (17)[f]	4 (8)
Treated with sonro, n (%)	4 (100)	9 (100)	6 (100)	22 (100)	6 (100)	47 (100)
Led to sonro discontinuation	0	0	0	2 (9)[b]	1 (17)[c]	3 (6)
Led to sonro dose reduction	0	0	0	1 (4)[g]	1 (17)[f]	2 (4)

[a]Due to intracranial hemorrhage. [b]Discontinued sonro and zanu due to myelodysplastic syndrome and meningococcal sepsis, n=1 each. [c]Discontinued sonro and zanu due to plasma cell myeloma. [d]COVID-19. [e]Reduced zanu during lead-in due to neutropenia, n=1; COVID-19, n=1. [f]Reduced sonro and zanu due to COVID-19, n=1. [g]Due to cellulitis.
Abbreviations: sonro, sonrotoclax; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.

Figure 2. TEAEs in ≥25% of All Patients and in Sonrotoclax RP2D Cohort[a]



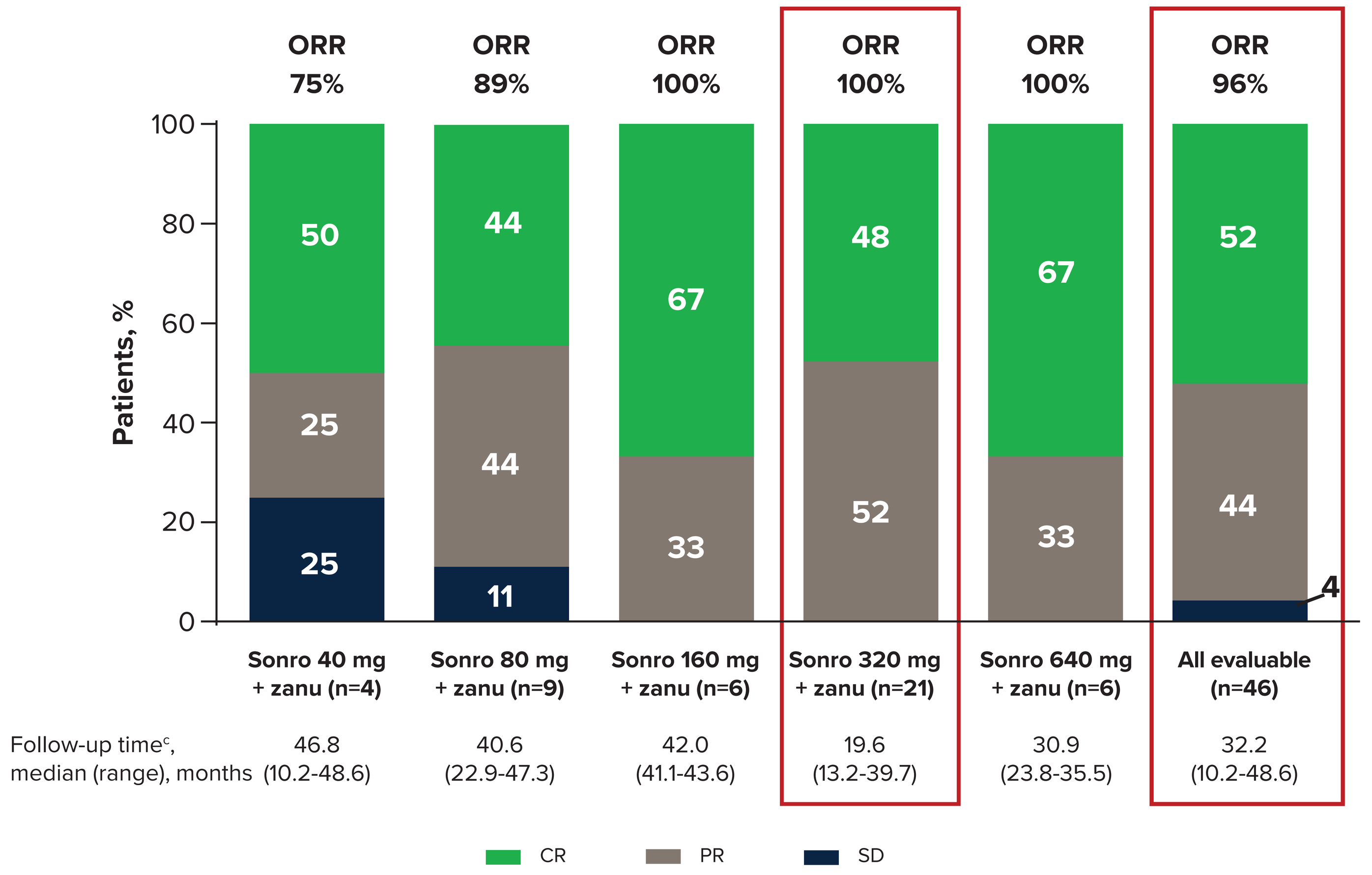
All Cohorts (N=47)
Median follow-up (range): 32.2 (10.2-48.6) months
Sonrotoclax 320 mg + Zanubrutinib (n=22)
Median follow-up (range): 19.6 (13.2-39.7) months
COVID-19
34
2
URTI
32
2
Contusion (bruising)
34
Diarrhea
34
Neutropenia[b]
4
28
Cough
30
Fatigue
30
Nausea
23
2
Neutropenia[b]
46
URTI
41
Diarrhea
36
Cough
32
Constipation
23
5
Contusion (bruising)
27
COVID-19
23
5
Thrombocytopenia[c]
23
5
0
10
20
30
40
50
Patients, %
Grade 1/2
Grade ≥3

[a]Grade is listed as worst grade experienced by patient on any drug. [b]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [c]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
Abbreviations: RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Efficacy

- In 46 response-evaluable patients, ORR was 96%, with a 52% complete response (CR)/complete response with incomplete count recovery (CRi) rate (**Figure 3**); in the 320-mg cohort, the ORR was 100%, with a 48% CR/CRi rate
- The median time to CR/CRi was 10.3 months (range, 5.3-42.4 months); in the 320-mg cohort, median time to CR was 8.5 months (range, 5.3-22.8 months)
- Of 7 evaluable patients with prior BTK inhibitor therapy, 5 achieved partial response and 1 achieved CR

Figure 3. Response Rates Across All Dose Levels[a,b]

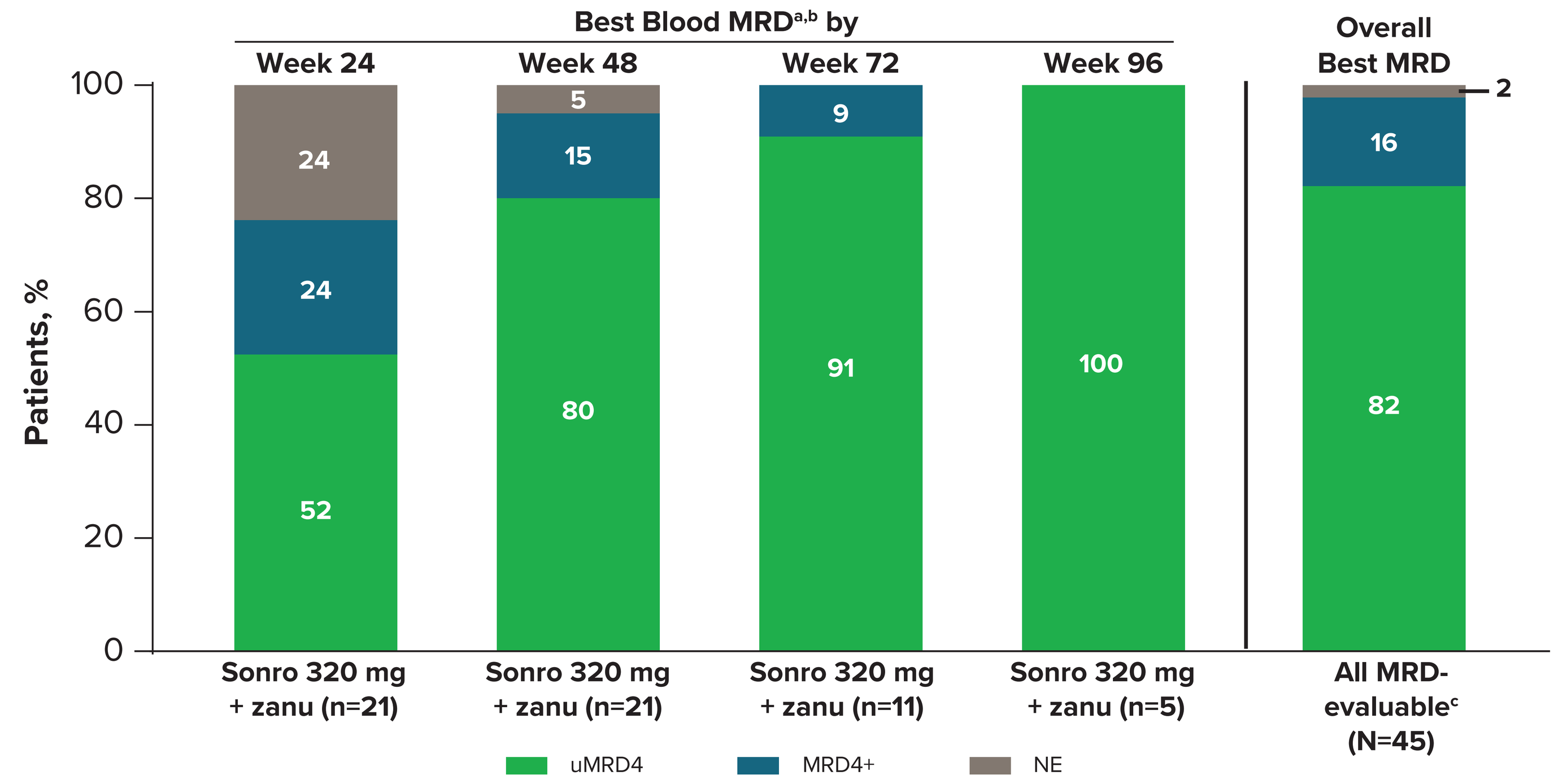


ORR 75%
ORR 89%
ORR 100%
ORR 100%
ORR 100%
ORR 96%
Patients, %
100
80
60
40
20
0
50
25
25
44
44
11
67
33
48
52
67
33
52
44
4
Sonro 40 mg + zanu (n=4)
Sonro 80 mg + zanu (n=9)
Sonro 160 mg + zanu (n=6)
Sonro 320 mg + zanu (n=21)
Sonro 640 mg + zanu (n=6)
All evaluable (n=46)
Follow-up time[c], median (range), months
46.8 (10.2-48.6)
40.6 (22.9-47.3)
42.0 (41.1-43.6)
19.6 (13.2-39.7)
30.9 (23.8-35.5)
32.2 (10.2-48.6)
CR
PR
SD

[a]Responses were assessed per 2008 iwCLL criteria and percentage of response is based on number of patients who had ≥1 post-baseline tumor assessment after sonrotoclax dosing. [b]ORR = PR-L or better. [c]For all patients as treated (n=47).
Abbreviations: BTK, Bruton tyrosine kinase; CR, complete response; ORR, overall response rate; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease; sonro, sonrotoclax; zanu, zanubrutinib.

- Of 45 MRD-evaluable patients, 37 (82%) achieved uMRD4 at the time of data cutoff (**Figure 4**)
- All patients in the 160-mg, 320-mg, and 640-mg cohorts who reached week 96 achieved uMRD4
- In the 320-mg cohort, 4/6 patients with del(17p) or *TP53* mutation had uMRD4 by week 48

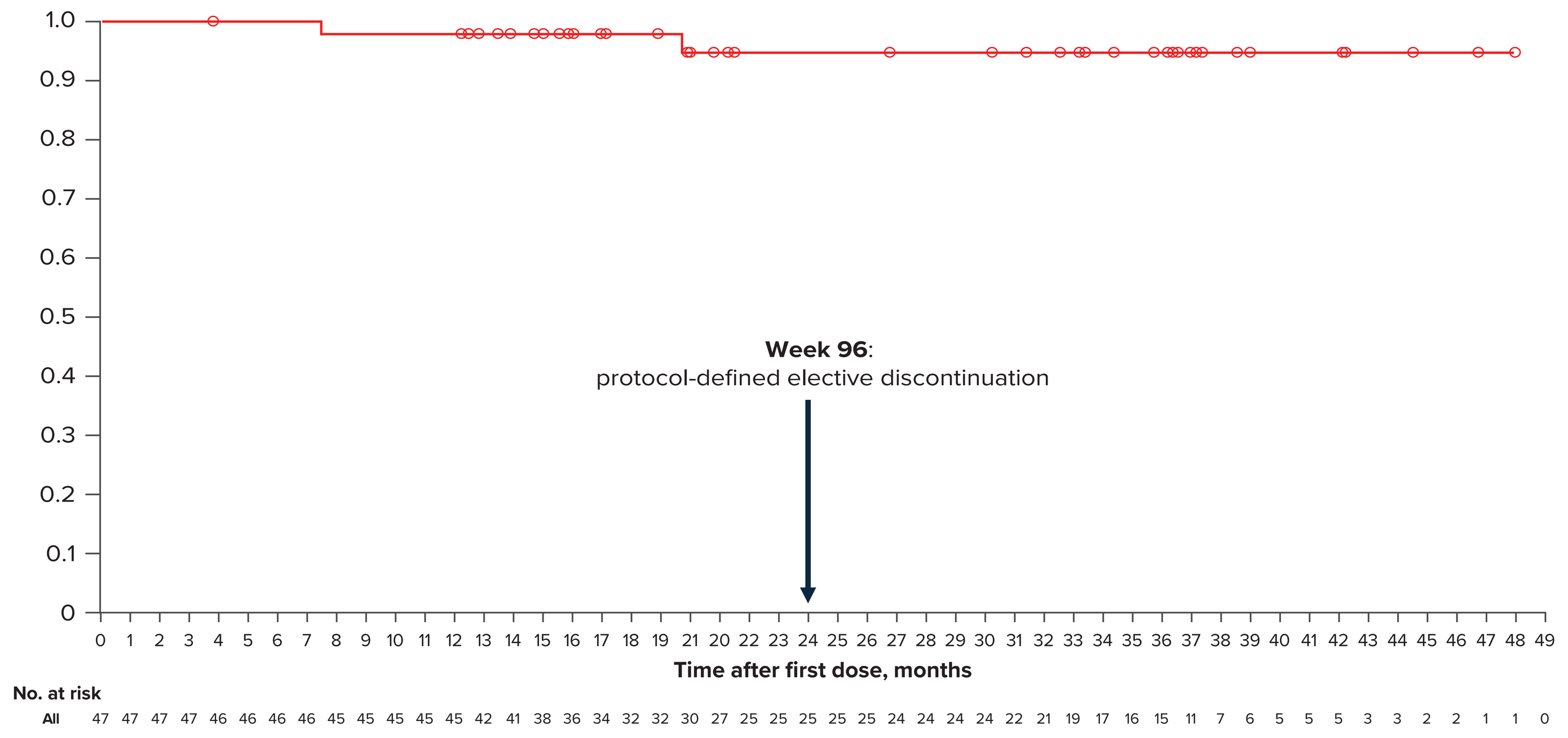
Figure 4. uMRD4 Rates Across All Dose Levels



Data cutoff: March 1, 2025.
[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 $\geq 10^{-4}$ CLL cells of total WBCs. MRD is best reported within a 2-week window following the week 24/week 48/week 72/week 96 day 1 MRD assessments. [b]Weeks 24, 48, 72, and 96 of treatment at target dose, following zanu monotherapy and sonro ramp-up to target dose. [c]All MRD-evaluable set includes patients with ≥1 post-baseline MRD sample or disease progression or death prior to MRD assessment, excluding those with baseline MRD level $<10^{-4}$.
Abbreviations: CLL, chronic lymphocytic leukemia; MRD, measurable residual disease; NE, not evaluable; sonro, sonrotoclax; uMRD, undetectable MRD; WBC, white blood cell; zanu, zanubrutinib.

- Thirteen patients electively discontinued treatment after at least 96 weeks of therapy; as of the data cutoff date, all were in remission and had a median time of 4.5 months off treatment (range, 1.8-12.3 months; **Figure 5**)
- Two progression-free survival (PFS) events occurred on study (40 mg, n=1; 320 mg, n=1) and the 30-month PFS rate was 94.7% (95% CI, 79.9%-98.7%; median follow-up, 30.5 months)

Figure 5. PFS Rate Across All Dose Levels



1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Week 96:
protocol-defined elective discontinuation
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 21 20 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49
Time after first dose, months
No. at risk
All 47 47 47 47 46 46 46 46 45 45 45 45 45 42 41 38 36 34 32 32 30 27 25 25 25 25 25 24 24 24 24 22 21 19 17 16 15 11 7 6 5 5 5 3 3 2 2 1 1 0

Abbreviation: PFS, progression-free survival.

REFERENCES

1. Hillmen P, et al. *J Clin Oncol*. 2019;37(30):2722-2729.
2. Guo Y, et al. *J Med Chem*. 2024;67(10):7836-7858.
3. Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.
4. Al-Sawaf O, et al. *Blood*. 2024;144(18):1924-1935.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. We would also like to thank Binghao Wu from BeOne Medicines Ltd for their work on the MRD analyses. This study was sponsored by BeOne Medicines Ltd. Medical writing support was provided by Brittany Gifford, PharmD, and Amanda Martin, PhD, of Nucleus Global, an Inizio company, and supported by BeOne Medicines.

DISCLOSURES

SSO: Honoraria: AbbVie, AstraZeneca, BeOne Medicines Ltd, Gilead, Janssen; Consulting or advisory role: AbbVie, AstraZeneca, BeOne Medicines Ltd, Janssen; Research funding: AbbVie, AstraZeneca, BeOne Medicines Ltd, Gilead, Janssen, Novartis, Pharmacyclics, Roche, Takeda; Other relationship (member of safety and data monitoring committee): Merck. **CST:** Honoraria: BeOne Medicines Ltd, Janssen, AbbVie, AstraZeneca, Gilead; Research funding: BeOne Medicines Ltd, Janssen, AbbVie. **MAA:** Honoraria, consulting or advisory role, speakers bureau: AbbVie, AstraZeneca, BeOne Medicines Ltd, Janssen, Gilead, Novartis, Takeda, Roche, CSL; Employee of the Walter and Eliza Hall Institute which receives milestone payments in relation to venetoclax to which I am entitled to a share. **AT:** Honoraria: BeOne Medicines Ltd, AbbVie, Lilly, Johnson & Johnson; Consulting or advisory role: AbbVie, BeOne Medicines Ltd, Lilly, AstraZeneca, Johnson & Johnson; Speakers bureau: BeOne Medicines Ltd, AbbVie, Johnson & Johnson, Lilly. **EV:** Speakers bureau: BeOne Medicines Ltd. **ML:** Consulting or advisory role: Janssen, BeOne Medicines Ltd, Sobi; Speakers bureau: Janssen, BeOne Medicines Ltd, AbbVie. **SS:** Honoraria, consulting or advisory role, research funding, speakers bureau, and travel, accommodations, or expenses: AbbVie, Amgen, AstraZeneca, BeOne Medicines Ltd, BMS, Galapagos, Gilead, GSK, Hoffmann-La Roche, Johnson & Johnson, Lilly, Novartis, Sunesis. **PB:** Consulting or advisory role: AbbVie. **SL:** Consulting or advisory role: BeOne Medicines Ltd; Speakers bureau: Pfizer; Travel, accommodations, expenses: BeOne Medicines Ltd, Pfizer, Janssen. **EG-B:** Consulting or advisory role: Kiowa, Sobi, AbbVie, AstraZeneca; Speakers bureau: Johnson & Johnson, AbbVie, AstraZeneca, Sobi; Travel, accommodations, expenses: AbbVie, AstraZeneca, BeOne Medicines Ltd. **MS:** Consultant: AbbVie, Genentech, AstraZeneca, Genmab, Janssen, BeOne Medicines Ltd, BMS, MorphoSys/Incyte, Kite Pharma, Lilly, Fate Therapeutics, Nurix, Merck; Research funding: Mustang Bio, Genentech, AbbVie, BeOne Medicines Ltd, AstraZeneca, Genmab, Morphosys/Incyte, Vincerx; Stock: Koi Biotherapeutics; Employment: BMS (spouse). **J-ZH:** Consulting or advisory role: AstraZeneca. **HE:** Consultant, research funding, honoraria, speakers bureau: AbbVie/Pharmacyclics, BeOne Medicines Ltd, Genentech, Incyte, MorphoSys; Research funding: AstraZeneca, Atara, BMS, Gilead/Kite Pharma, Juno. **YF, JH, SP:** Employment and may own stock: BeOne Medicines Ltd. **CYC:** Consulting, advisory board, honoraria: Roche, Janssen, Gilead, AstraZeneca, Lilly, BeOne Medicines Ltd, Menarini, Dizal, AbbVie, Genmab, Sobi, CRISPR Therapeutics, BMS, Regeneron; Speakers bureau: Janssen, AstraZeneca, BeOne Medicines Ltd, Genmab, Abbvie, Roche, MSD; Research funding: BMS, Roche, AbbVie, MSD, Lilly; Travel expenses: Lilly, BeOne Medicines Ltd. **AA, DW:** No disclosures.

CORRESPONDENCE: Stephen S. Opat, stephen.opat@monash.edu

Presented at the 2025 International Workshop on CLL; September 12-15, 2025, Krakow, Poland
Data originally presented at the EHA 2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S159.