

Updated Safety and Efficacy of All-Oral Sonrotoclax + Zanubrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, Including Patients With del(17p)/TP53

PS1697

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} Binghao Wu,²⁰ Gabriel Man,²¹ Yiqian Fang,²⁰ Sheel Patel,²¹ Remus Vezen,²¹ Chan Y. Cheah²²⁻²⁴

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

CONCLUSIONS

- With a median study follow-up of 40.6 mo, sonrotoclax + zanubrutinib was tolerable and demonstrated substantial antitumor activity in the R/R CLL/SLL population, including those who were BTK inhibitor-pretreated and those with high-risk features, such as TP53 mutation, del(17p), or unmutated IGHV
 - No cases of TLS occurred
 - Response rates were high and deepened over time, with a 100% ORR and 52.4% CR rate observed in the sonrotoclax 320-mg/RP2D cohort
 - High rates of blood uMRD4 were seen by week 24 of combination therapy and increased over time, with 85.7% of the sonrotoclax 320-mg/RP2D cohort achieving uMRD4 by week 72
 - Across all cohorts, 24 of 25 patients who electively discontinued treatment remain in remission, with a median time off treatment of 13.8 mo, including all patients in the sonrotoclax 320-mg/RP2D cohort
- These results continue to support the development of all-oral, time-limited treatment with sonrotoclax + zanubrutinib in this population with substantial unmet need, including those with high-risk disease features and poor outcomes

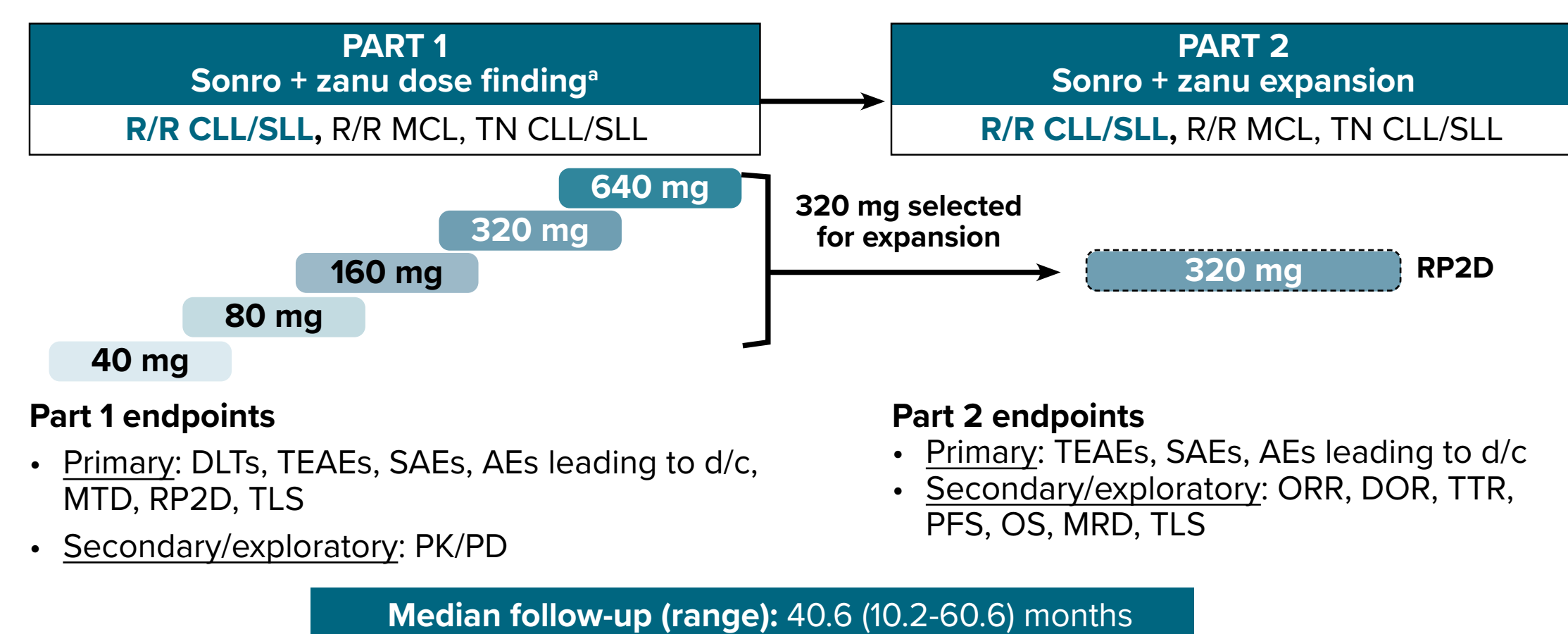
INTRODUCTION

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is an indolent B-cell malignancy characterized by recurrent cycles of relapse following remission¹
 - Fixed-duration therapies have emerged as an effective treatment for relapsed/refractory (R/R) CLL/SLL, leading to the US approval of venetoclax + acalabrutinib²; however, novel treatments that improve safety and tolerability while maintaining response depth and durability are needed
- Sonrotoclax (BGB-11417), a next-generation B-cell lymphoma 2 (BCL2) inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation^{3,4}
 - In May 2026, sonrotoclax received accelerated approval from the US FDA for patients with R/R MCL who had previously received ≥2 lines of therapy, including a BTK inhibitor⁵
- Zanubrutinib, a highly selective and potent next-generation Bruton tyrosine kinase (BTK) inhibitor approved for CLL/SLL, has demonstrated superior progression-free survival (PFS) and fewer cardiac adverse events (AEs) in a phase 3 head-to-head trial of zanubrutinib vs ibrutinib in patients with R/R CLL/SLL⁶
- Here, updated safety and efficacy data are reported from the phase 1/1b BGB-11417-101 study of sonrotoclax + zanubrutinib combination therapy in patients with R/R CLL/SLL

METHODS

- BGB-11417-101 (NCT04277637) is an ongoing global, phase 1/1b, dose selection and expansion study evaluating sonrotoclax as monotherapy or in combination with zanubrutinib and/or obinutuzumab in patients with mature B-cell malignancies (Figure 1)
- Zanubrutinib monotherapy (320 mg once daily [QD] or 160 mg twice daily) was administered for 8-12 weeks, followed by sonrotoclax + zanubrutinib until disease progression, unacceptable toxicity, or protocol-defined elective discontinuation after week 96
- Sonrotoclax target doses (40, 80, 160, 320, or 640 mg QD) were achieved through gradual dose ramp-up over approximately 4 weeks to mitigate the risk of tumor lysis syndrome (TLS)

Figure 1. BGB-11417-101 Study Design



¹The safety monitoring committee reviewed dose-level cohort data before dose escalation.
Abbreviations: AE, adverse event; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; d/c, discontinuation; DLT, dose-limiting toxicity; DOR, duration of response; MCL, mantle cell lymphoma; MRD, measurable residual disease; MTD, maximum tolerated dose; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PK/PD, pharmacokinetics/pharmacodynamics; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; SAE, serious adverse event; sonro, sonrotoclax; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; TN, treatment naïve; TTR, time to response; zanu, zanubrutinib.

RESULTS

- As of March 1, 2026, a total of 47 patients with R/R CLL/SLL were enrolled, including 22 patients in the sonrotoclax 320-mg/RP2D cohort (Table 1)
- At baseline, 37.2% (16/43) of patients had TP53 mutation and/or del(17p) and 73.9% (34/46) had unmutated immunoglobulin heavy chain variable region (IGHV)
- Seven patients (14.9%) had received prior BTK inhibitor therapy
- At the data cutoff, 14 patients (29.8%) remained on treatment; of 33 patients who discontinued sonrotoclax, 25 (75.8%) did so due to protocol-defined elective discontinuation
 - As of the data cutoff date, 24/25 (96.0%) who electively discontinued were in remission and had a median time off treatment of 13.8 mo (range, 1.8-24.3 mo)

Table 1. Baseline Characteristics

Parameters	Sonro 320 mg/RP2D + zanu (n=22)	All (N=47)
Study follow-up, median (range), mo	40.6 (10.2-60.6)	
Age, median (range), y	67.0 (36-76)	65.0 (36-76)
Male, n (%)	18 (81.8)	35 (74.5)
ECOG PS, n (%)		
0	11 (50.0)	28 (59.6)
1	10 (45.5)	17 (36.2)
2	1 (4.5)	2 (4.3)
Risk status, n/tested (%)		
del(17p)	3/18 (16.7)	11/42 (26.2)
TP53 mutation ^a	6/22 (27.3)	14/46 (30.4)
del(17p) and/or TP53 mutation ^a	7/20 (35.0)	16/43 (37.2)
Unmutated IGHV, n/tested (%)	17/21 (81.0)	34/46 (73.9)
No. of prior lines of therapy, median (range)	1 (1-3)	1 (1-3)
Prior BTK inhibitor treatment, n (%)	3 (13.6)	7 (14.9)
Duration, median (range), mo	38.1 (34.2-49.1)	34.2 (1.6-86.6)

Data cutoff: March 1, 2026.
^aTP53 mutation was defined as ≥5% variant allele frequency.
Abbreviations: BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology group performance status; IGHV, immunoglobulin heavy chain variable region; RP2D, recommended phase 2 dose; sonro, sonrotoclax; zanu, zanubrutinib.

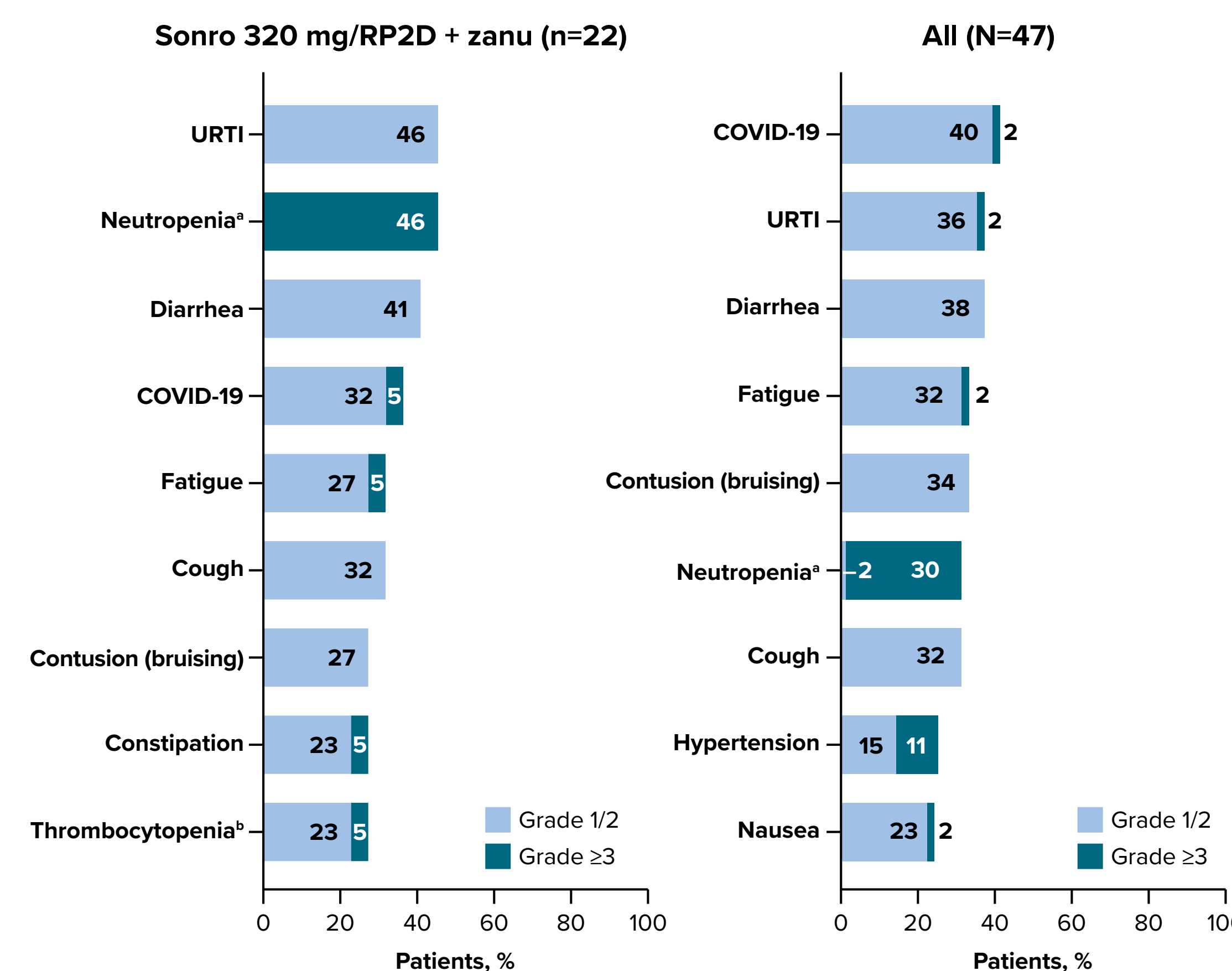
- Across all cohorts, the most common any-grade treatment-emergent adverse events (AEs) were COVID-19 (42.6%), upper respiratory tract infection (38.3%), and diarrhea (38.3%) (Figure 2)
- The most common grade ≥3 AE was neutropenia (29.8%)
- One patient in the sonrotoclax 40-mg cohort had an AE leading to death (histiocytic sarcoma; not related to study treatment) >30 days from last dose (Table 2)
- No laboratory or clinical TLS occurred

Table 2. Safety Summary

Patients, n (%)	Sonro 320 mg/RP2D + zanu (n=22)	All (N=47)
Any TEAE	22 (100)	46 (97.9)
Grade ≥3	18 (81.8)	34 (72.3)
Serious	11 (50.0)	23 (48.9)
Leading to death	0 (0)	1 (2.1) ^a
Leading to zanu discontinuation	2 (9.1)	6 (12.8) ^b
Leading to sonro discontinuation	2 (9.1)	5 (10.6) ^c

^aOne patient in the sonro 40-mg cohort had a TEAE leading to death (histiocytic sarcoma) that occurred >30 days from last dose. ^bZanu discontinuations (n=6): histiocytic sarcoma (sonro cohort: 40 mg), intracranial hemorrhage (80 mg), meningococcal sepsis (320 mg), myelodysplastic syndrome (320 mg), knee pain (640 mg), and myeloma (640 mg). ^cSonro discontinuations (n=5): histiocytic sarcoma (sonro cohort: 40 mg), meningococcal sepsis (320 mg), myelodysplastic syndrome (320 mg), knee pain (640 mg), and myeloma (640 mg).
Abbreviations: RP2D, recommended phase 2 dose; sonro, sonrotoclax; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.

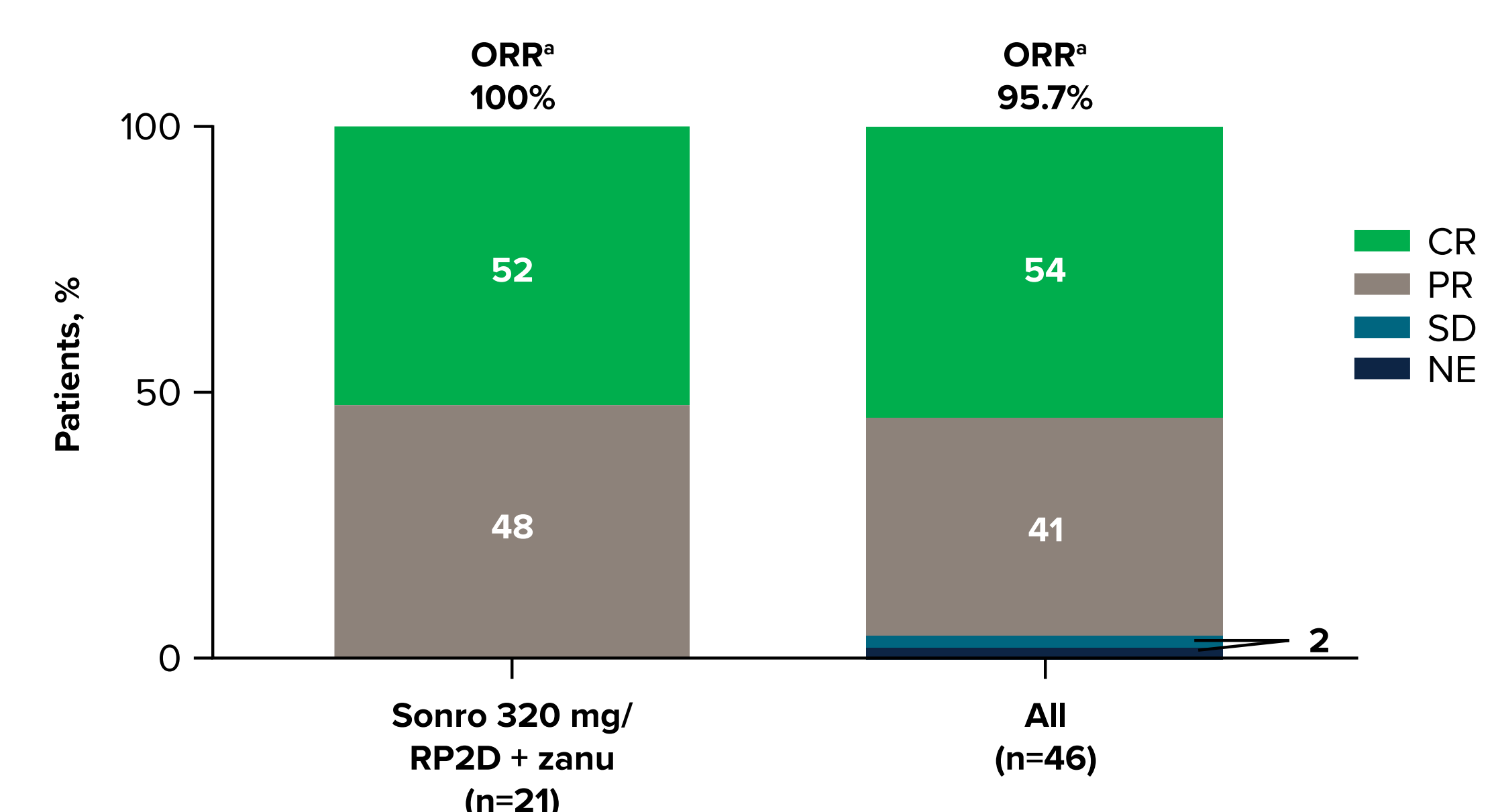
Figure 2. Treatment-Emergent AEs in ≥25% of Patients



^aNeutropenia includes PTs neutrophil count decreased and neutropenia; ^bThrombocytopenia includes PTs platelet count decreased and thrombocytopenia.
Abbreviations: AE, adverse event; PT, preferred term; RP2D, recommended phase 2 dose; sonro, sonrotoclax; URTI, upper respiratory tract infection; zanu, zanubrutinib.

- Among 46 efficacy-evaluable patients across all doses, the overall response rate (ORR) was 95.7%, with a complete response (CR) rate of 54.3% (Figure 3)
 - Among 21 efficacy-evaluable patients in the sonrotoclax 320-mg/RP2D cohort, ORR was 100% and CR rate was 52.4%
- Median follow-up was 40.6 mo (range, 10.2-60.6 mo); median time to CR was 10.5 mo (range, 5.3-42.6 mo)
 - In the sonrotoclax 320-mg/RP2D cohort, median time to CR was 9.9 mo (range, 5.3-22.8 mo)
- Among seven evaluable patients with prior BTK inhibitor therapy, five achieved partial response, one achieved CR, and one was not evaluable

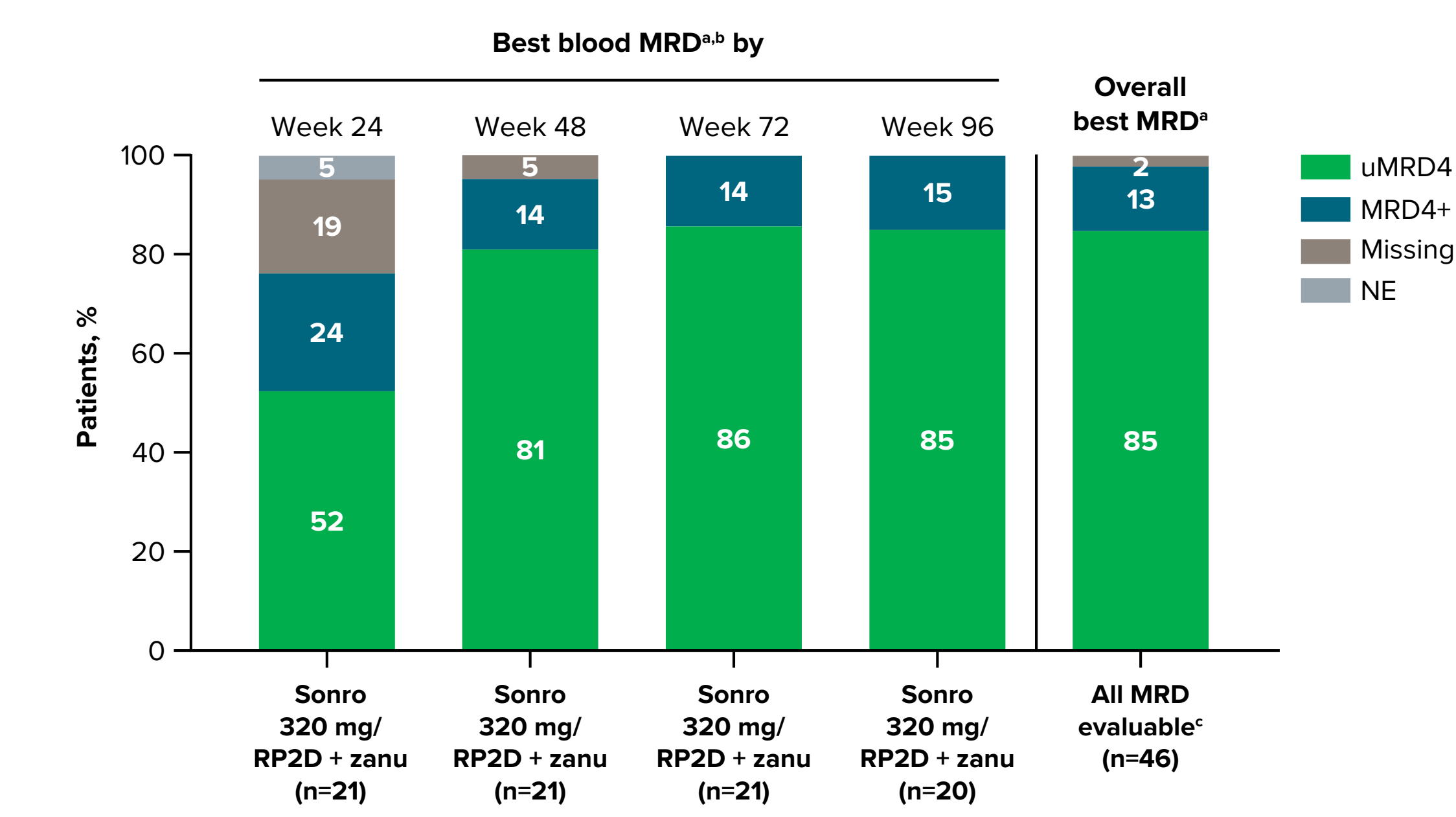
Figure 3. Overall Response Rates



^aDefined as PR with lymphocytosis or better per International Workshop on CLL 2018 guidelines.
Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; NE, not evaluable; ORR, overall response rate; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease; sonro, sonrotoclax; zanu, zanubrutinib.

- For 46 measurable residual disease (MRD)-evaluable patients, the best rate of undetectable MRD at 10⁴ sensitivity (uMRD4) was 84.8% at the data cutoff (Figure 4)
 - In the sonrotoclax 320-mg/RP2D cohort, best uMRD4 rates were 52.4%, 81.0%, and 85.0% by weeks 24, 48, and 96, respectively
 - Among patients with del(17p) and/or TP53 mutation in the sonrotoclax 320-mg/RP2D cohort, 66.7% (4/6) achieved uMRD4 by week 48

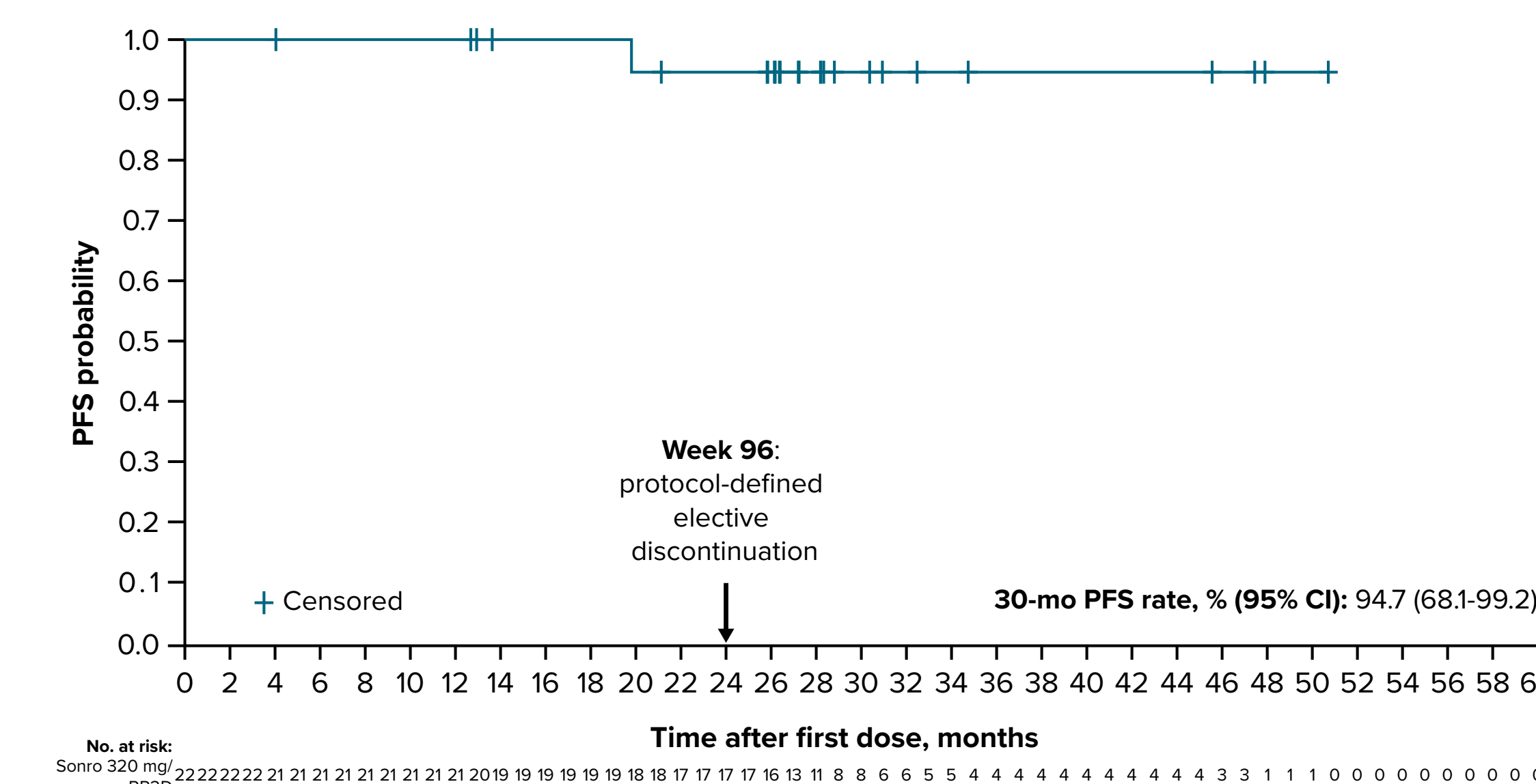
Figure 4. Landmark uMRD4 Rates: Sonrotoclax 320-mg/RP2D Cohort



^aFlow cytometry-based assay of ERIC-recommended core panel markers. uMRD4 and MRD4+ were defined as <1 and ≥1 CLL cell per 10⁴ total white blood cells, respectively. MRD is best reported within a 4-week window following week 24, 48, 72, and 96 day 1 assessments. ^bWeeks 24, 48, 72, and 96 at sonro target dose following zanu monotherapy. ^cIncludes patients with ≥1 postbaseline MRD status or disease progression or death prior to MRD assessment, excluding those with baseline MRD level <10⁴.
Abbreviations: CLL, chronic lymphocytic leukemia; ERIC, European Research Initiative on CLL; MRD, measurable residual disease; NE, not evaluable; RP2D, recommended phase 2 dose; sonro, sonrotoclax; uMRD, undetectable measurable residual disease; zanu, zanubrutinib.

- Among the sonrotoclax 320-mg/RP2D cohort, 13 patients electively discontinued treatment after ≥96 weeks of combination therapy
 - As of the data cutoff date, all were in remission and had a median time off treatment of 4.5 mo (range, 1.8-17.0 mo) (Figure 5)
- With a median follow-up of 40.6 mo (range, 10.2-60.6 mo), the 36-mo PFS rate was 95.5% (95% CI, 83.2%-98.9%) across all dose cohorts

Figure 5. Progression-Free Survival: Sonrotoclax 320-mg/RP2D Cohort



Abbreviations: PFS, progression-free survival; RP2D, recommended phase 2 dose; sonro, sonrotoclax.

REFERENCES

- Robak T, et al. *J Clin Med*. 2025;14(2):8247.
- Venclaxta (venetoclax). Prescribing information. AbbVie, Inc; 2026.
- Guo Y, et al. *J Med Chem*. 2024;67(10):7836-7858.
- Liu J, et al. *Blood*. 2024;143(18):1825-1836.
- Beqalzi (sonrotoclax). Prescribing information. BeOne Medicines, Ltd; 2026.
- Guo Y, et al. *N Engl J Med*. 2023;388(4):319-332.

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 support was provided by Amy Ryan, 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 (payable to institution): AbbVie, AstraZeneca, BeOne Medicines, Ltd, Gilead, Janssen, Novartis, Pharmacosys, Roche, Takeda; Other relationship (member of safety and data monitoring committee): Merck. **CSF:** Honoraria: BeOne Medicines, Ltd, Janssen, AbbVie, AstraZeneca, Gilead, Lilly, Merck; 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. **Employment:** the Walter and Eliza Hall Institute, which receives milestone payments in relation to venetoclax to which MAA is entitled to share. **AD:** Honoraria: AbbVie, Johnson & Johnson, AstraZeneca, Lilly, BeOne Medicines, Ltd; Consulting or advisory role: AstraZeneca, AbbVie, BeOne Medicines, Ltd, Lilly, Johnson & Johnson; Speakers bureau: BeOne Medicines, Ltd, AbbVie, Johnson & Johnson, Lilly. **EV:** Speakers bureau: BeOne Medicines, Ltd, AbbVie, AstraZeneca, BeOne Medicines, Ltd, Lilly, Johnson & Johnson; Speakers bureau: BeOne Medicines, Ltd, AbbVie, Johnson & Johnson, Lilly. **BE:** Speakers bureau: BeOne Medicines, Ltd, AbbVie, AstraZeneca, BeOne Medicines, Ltd, Lilly, Johnson & Johnson; Speakers bureau: BeOne Medicines, Ltd, AbbVie, Johnson & Johnson, Lilly. **BE:** Speakers bureau: Pfizer, travel, accommodations, expenses: BeOne Medicines, Ltd, AbbVie. **EG-B:** Consulting or advisory role: Kowa, Sobi, AbbVie, AstraZeneca, Speakers bureau: Johnson & Johnson, AbbVie, AstraZeneca, Sobi; Travel, accommodations, expenses: AbbVie, AstraZeneca, BeOne Medicines, Ltd, BMS, Galapagos, Gilead, GSK, Hoffmann-La Roche, Johnson & Johnson, Lilly, Novartis, Sunesis. **PB:** Consulting or advisory role: AbbVie; Research funding (payable to institution): BeOne Medicines, Ltd, SLL; Speakers bureau: Pfizer; Travel, accommodations, expenses: BeOne Medicines, Ltd, AbbVie. **ML:** Consulting or advisory role: Kowa, Sobi, AbbVie, AstraZeneca, Speakers bureau: Johnson & Johnson, AbbVie, AstraZeneca, Sobi; Travel, accommodations, expenses: AbbVie, AstraZeneca, BeOne Medicines, Ltd, BMS. **MS:** Consulting, advisory boards, steering committees, or data safety monitoring committees: AbbVie, Ascertainment, Genentech, AstraZeneca, Genmab, Janssen, BeOne Medicines, Ltd, BMS, MorphoSys/Incyte, Kite Pharma, Lilly, Fate Therapeutics, Nuvia, Merck, Pfizer, Pierre Fabre; Research funding: Genentech, BeOne Medicines, Ltd, AstraZeneca, Genmab, MorphoSys/Incyte, Sanofi Bioclinical, Nuvia, Merck, Janssen; Employment (unpaid): BMS; Stock options: Kite Biopharmaceuticals. **PZH:** Consulting or advisory role: AstraZeneca. **HE:** Consultant, research funding, honoraria, speakers bureau: AbbVie/Pharmacosys, BeOne Medicines, Ltd, Genentech, Incyte, MorphoSys; Research funding: AstraZeneca, Alara, BMS, Gilead/Kite Pharma, Juno. **BW, GM, YF, SP:** Employment and may own stock: BeOne Medicines, Ltd. **RV:** Employment: BeOne Medicines, Ltd; Stock: BeOne Medicines, Ltd, AbbVie, Gilead. **CTC:** Consulting, advisory board, honoraria: Roche, Janssen, Gilead, AstraZeneca, Lilly, BeOne Medicines, Ltd, Menarini, Dical, AbbVie, Genmab, Sobi, CERSPR 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.