Updated Results From the Phase 1 Study of Sonrotoclax (BGB-11417), a Novel BCL2 Inhibitor, in Combination With Zanubrutinib for Relapsed/Refractory CLL/SLL Demonstrate Deep and Durable Responses

Chan Y. Cheah,[1-3] Constantine S. Tam,[4] Mary Ann Anderson,[5,6] Alessandra Tedeschi,[7] Emma Verner,[8,9] Masa Lasica,[10] Alejandro Arbelaez,[11] Stephan Stilgenbauer,[12] Peter Browett,[13] Sophie Leitch,[14] Eva González-Barca,[15] Mazyar Shadman,[16,17] Jing-Zhou Hou,[18] Herbert Eradat,[19] David Westerman,[20,21] Yiqian Fang,[22] James Hilger,[23] Sheel Patel,[23] Stephen S. Opat[24]

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

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Introduction

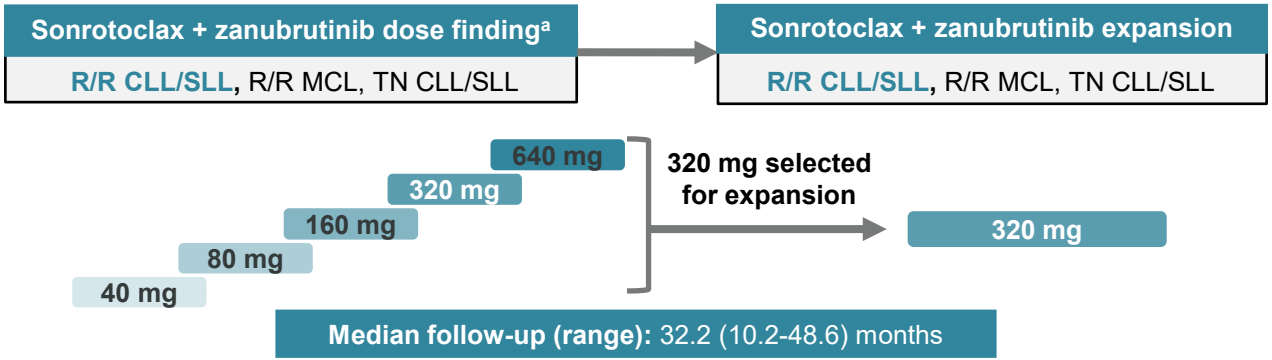
- CLL/SLL remains incurable as many treated patients experience relapse,[1] necessitating further treatment with novel agents
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug 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 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 (NCT04277637)

BCL2, B-cell lymphoma; BTK, Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; R/R, relapsed/refractory.

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.

BGB-11417-101 (NCT04277637) Study Design

- 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
  - Data from R/R CLL/SLL cohorts treated with sonrotoclax + zanubrutinib are the focus of this presentation
- The primary endpoints are safety per NCI CTCAE v5.0, MTD, and RP2D
- For this R/R CLL/SLL cohort, treatment consists of 8-12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID), then zanubrutinib + sonrotoclax until disease progression, intolerance, or elective discontinuation
- 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)



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

BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; QD, once daily; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; TN, treatment naive.

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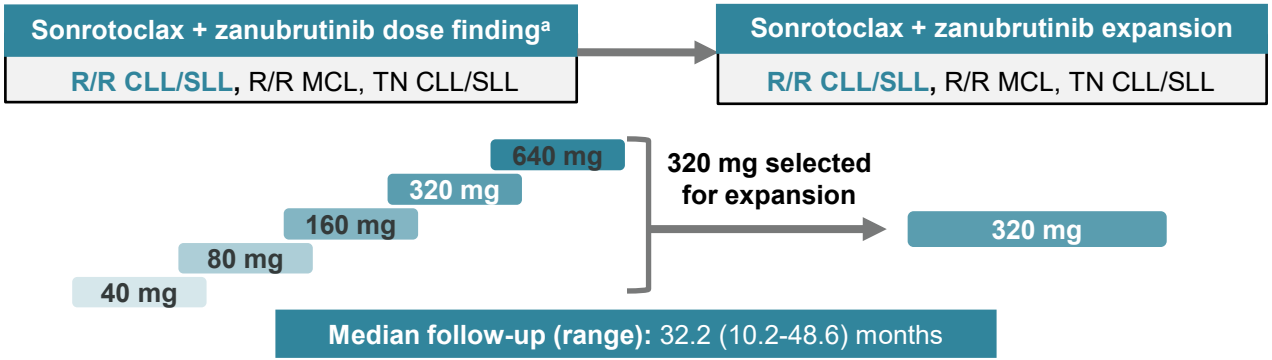

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Baseline Characteristics and Demographics

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						
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)
del(17p), n/tested (%)	3/4 (75)	4/8 (50)	1/6 (17)	3/18 (17)	0	11/42 (26)
del(17p) and/or *TP53* mutation[a], n/tested (%)	**3/4 (75)**	**5/8 (63)**	**1/6 (17)**	**7/19 (37)**	**0**	**16/42 (38)**
Unmutated IGHV, n/tested (%)	**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* mutations defined as ≥5% variant allele frequency. [b]BTK inhibitor was the last prior therapy for 7 patients; all discontinued due to toxicity.

BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology group performance status; sonro, sonrotoclax; zanu, zanubrutinib.

TEAE Summary

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

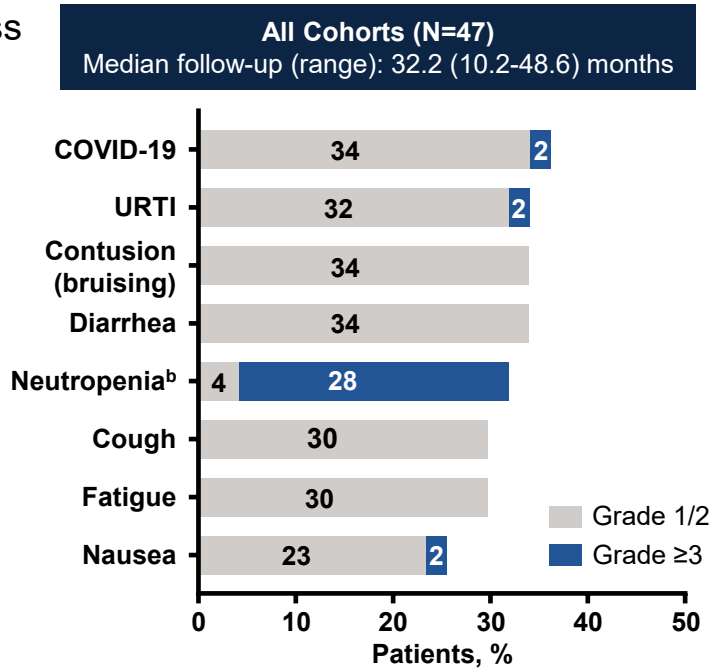
Patients, n (%)	Sonro 40 mg + Zanu (n=4)	Sonro 80 mg + Zanu (n=9)	Sonro 160 mg + Zanu (n=6)	Sonro 320 mg + Zanu (n=22)	Sonro 640 mg + Zanu (n=6)	All (N=47)
Any TEAEs	4 (100)	9 (100)	6 (100)	22 (100)	5 (83)	46 (98)
Grade ≥3	1 (25)	7 (78)	3 (50)	18 (82)	3 (50)	32 (68)
Serious TEAEs	1 (25)	3 (33)	3 (50)	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)

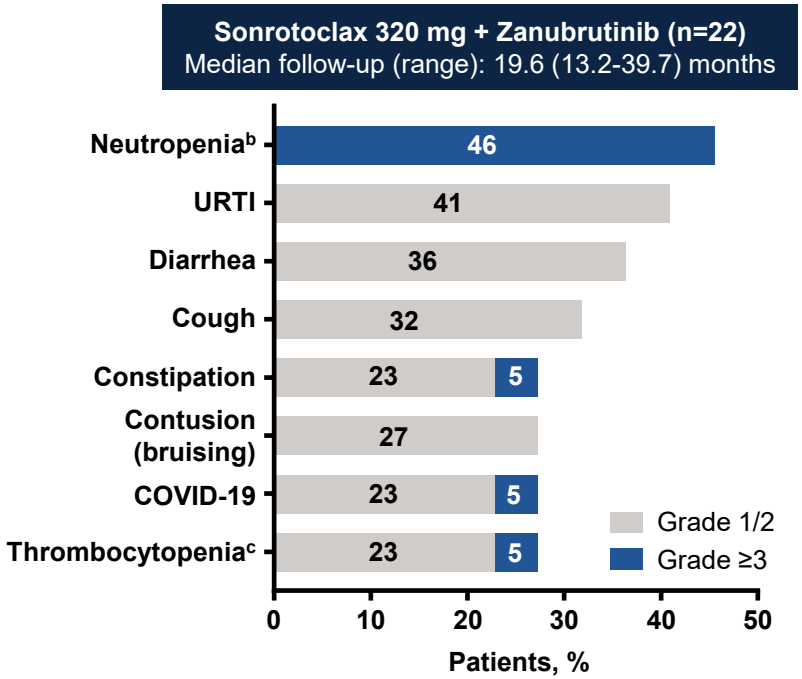
[a]Due to intracranial hemorrhage. [b]Discontinued sonro and zanu due to myelodysplastic syndrome and meningococcal sepsis, n=1 each. [c]Discontinued sonro and zanu due to plasma cell myeloma. [d]COVID-19. [e]Reduced zanu during lead-in due to neutropenia, n=1; COVID-19, n=1. [f]Reduced sonro and zanu due to COVID-19, n=1. [g]Due to cellulitis.
DLT, dose-limiting toxicity; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose; sonro, sonrotoclax; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.

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

- Toxicities were comparable across all dose levels
- No TLS or febrile neutropenia
- No dose reductions occurred due to diarrhea

TEAEs in ≥25% of all patients and those treated at sonrotoclax RP2D of 320 mg[a]

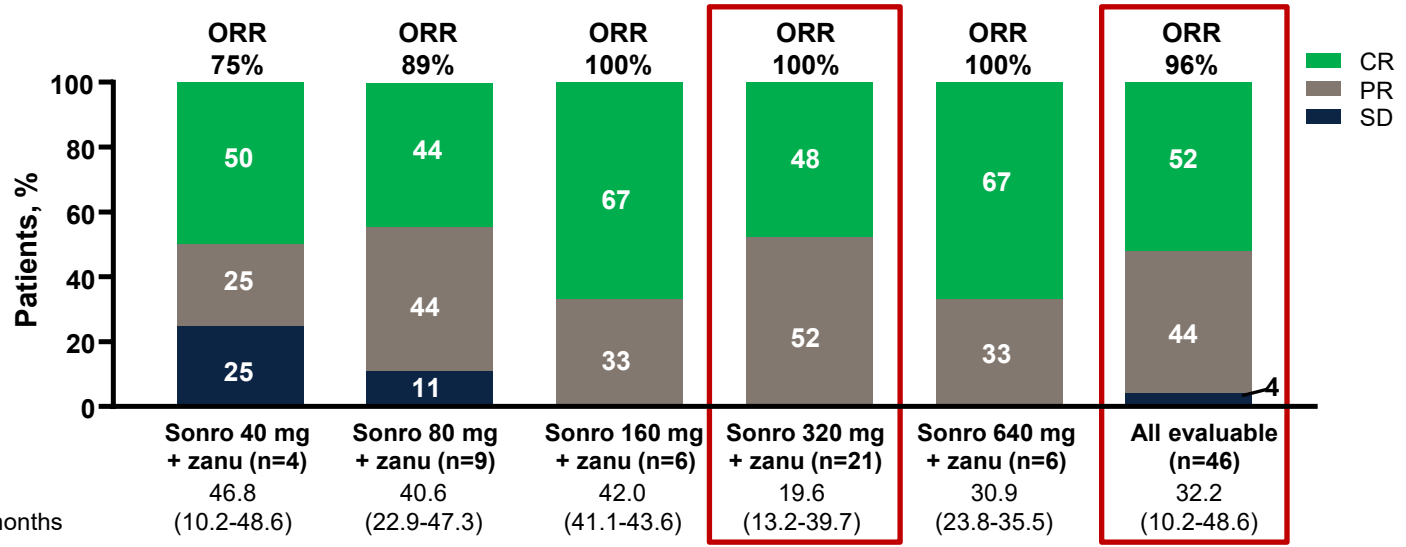




[a]Grade is listed as worst grade experienced by patient on any drug. [b]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*.
[c]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
RP2D, recommended phase 2 dose; TEAE, treatment-emergent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

Sonrotoclax + Zanubrutinib Achieved High Response Rates Across All Dose Levels

- With a median study follow-up of 32.2 months, the ORR was 96%, with a 52% CR/CRi rate across all doses[a,b]
  - In the 320-mg cohort, the ORR was 100%, with a 48% CR/CRi rate
- The median time to CR or CRi was 10.3 months (range, 5.3-42.4 months)
  - In the 320-mg cohort, the 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 PR and 1 achieved CR

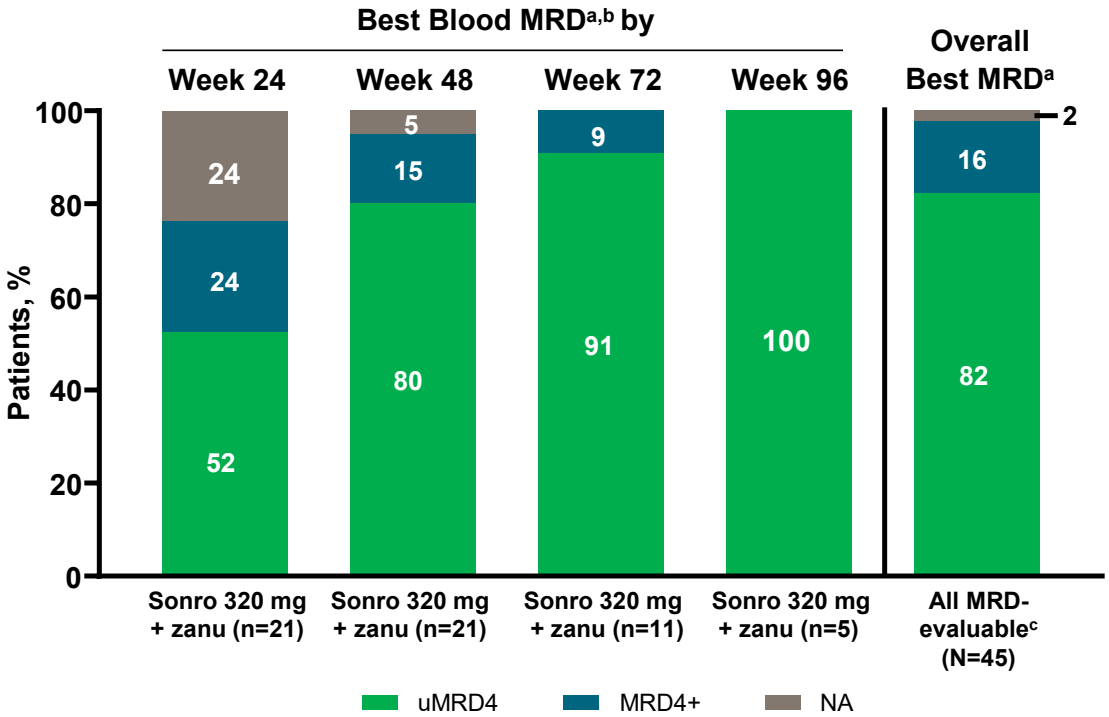


Follow-up time[c], median (range), months	Sonro 40 mg + zanu (n=4)	Sonro 80 mg + zanu (n=9)	Sonro 160 mg + zanu (n=6)	Sonro 320 mg + zanu (n=21)	Sonro 640 mg + zanu (n=6)	All evaluable (n=46)
	46.8 (10.2-48.6)	40.6 (22.9-47.3)	42.0 (41.1-43.6)	19.6 (13.2-39.7)	30.9 (23.8-35.5)	32.2 (10.2-48.6)

[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).
BTK, Bruton tyrosine kinase; CR, complete response; CRi, complete response with incomplete hematologic recovery; ORR, overall response rate; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease; sonro, sonrotoclax; zanu, zanubrutinib.

Sonrotoclax + Zanubrutinib Demonstrated Early and High uMRD4 Rates, Which Deepened Over Time

- Of 45 MRD-evaluable patients, 37 (82%) achieved uMRD4 at the time of data cutoff
- 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



Data cutoff: March 1, 2025.

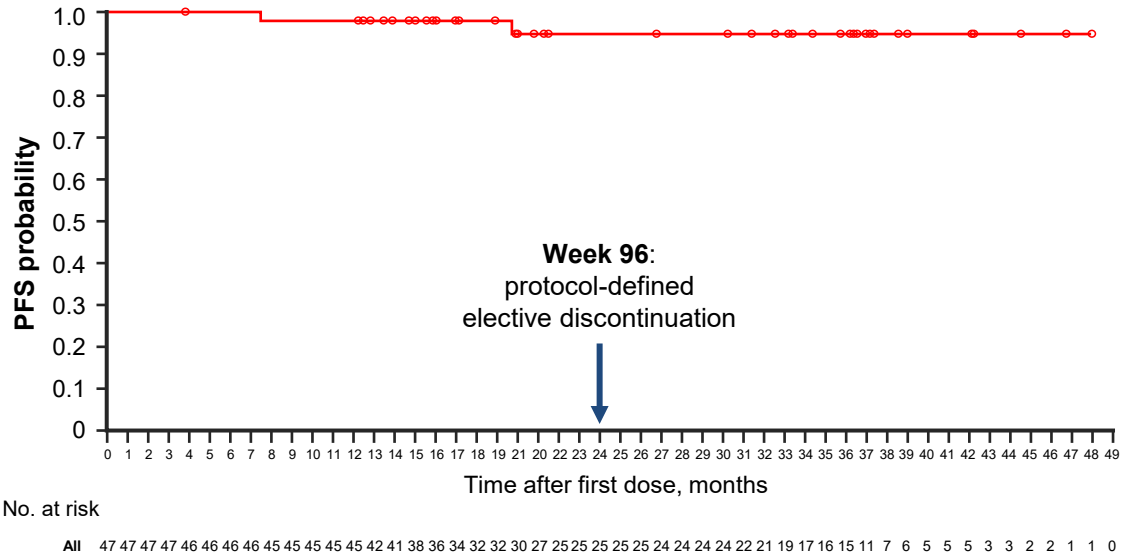
[a]Measured by an ERIC-approved flow cytometry method with 10^{-4} sensitivity. uMRD4 defined as $<10^{-4}$ CLL cells of total WBCs. MRD4+ defined as $\geq 10^{-4}$ CLL cells of total WBCs. MRD is best reported within a 2-week window following the week 24/week 48/week 72/week 96 day 1 MRD assessments. [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 $<10^{-4}$.

CLL, chronic lymphocytic leukemia; MRD, measurable residual disease; sonro, sonrotoclax; uMRD, undetectable MRD; WBC, white blood cell; zanu, zanubrutinib.

Substantial PFS Rate is Observed Across All Dose Levels and Risk Factors

- 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)
- With median study follow-up time of 32.2 months, only 2 PFS events occurred on study:
  - 40 mg: del(17)p+
  - 320 mg: del(17)p+
- The 30-month PFS rate was 94.7% (95% CI, 79.9%-98.7%; median follow-up, 30.5 months)



CR, complete response; MRD, measurable residual disease; uMRD, undetectable measurable residual disease; PFS, progression-free survival.

With Longer Follow-Up, Sonrotoclax + Zanubrutinib Continued to Demonstrate Compelling Safety and Efficacy in R/R CLL/SLL

- 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 overtime
  - 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**

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