Results From the Phase 1 Study of the Novel BCL2 Inhibitor Sonrotoclax in Combination with Zanubrutinib for Relapsed/Refractory CLL/SLL Show Deep and Durable Responses

Stephen Opat,[1] Mary Ann Anderson,[2,3] Alessandra Tedeschi,[4] Emma Verner,[5,6] Masa Lasica,[7] Alejandro Arbelaez,[8] Stephan Stilgenbauer,[9] Peter Browett,[10] Sophie Leitch,[11] Eva Gonzalez-Barca,[12] Mazyar Shadman,[13,14] Jing-Zhou Hou,[15] Herbert Eradat,[16] Shuo Ma,[17] David Westerman,[18,19] Yiqian Fang,[20] James Hilger,[21] Sheel Patel,[21] Wei Ding,[21] Haiyi Guo,[22] Constantine S. Tam[23]

[1]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [2]Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [3]The Walter and Eliza Hall Institute, Melbourne, VIC, Australia; [4]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [5]Concord Repatriation General Hospital, Concord, NSW, Australia; [6]University of Sydney, Sydney, NSW, Australia; [7]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [8]Pindara Private Hospital, Benowa, QLD, Australia; [9]Division of CLL, Internal Medicine III, Ulm University, Ulm, Germany; [10]Auckland City Hospital, Grafton, Auckland, New Zealand; [11]Te Whatu Ora, Health New Zealand, Waitemata, Auckland, New Zealand; [12]Institut Català d'Oncologia Hospitalet, Universitat de Barcelona, IDIBELL, Barcelona, Spain; [13]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [14]University of Washington, Seattle, WA, USA; [15]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [16]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; [17]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [18]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [19]University of Melbourne, Melbourne, VIC, Australia; [20]BeiGene (Beijing) Co, Ltd, Beijing, China; [21]BeiGene USA, Inc, San Mateo, CA, USA; [22]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [23]Alfred Hospital and Monash University, Melbourne, VIC, Australia

Presented at the EHA2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain

Disclosures for Stephen Opat

- AbbVie (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees); Antengene (consulting fees); AstraZeneca (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees); BeiGene (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees); BMS (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees); CSL Behring (consulting fees); Gilead (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees); Janssen (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees); Merck (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees); Novartis (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees); Pharmacyclics (research funding); Roche (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees); Takeda (consulting fees, research funding, honoraria, membership on an entity's board of directors or advisory committees)

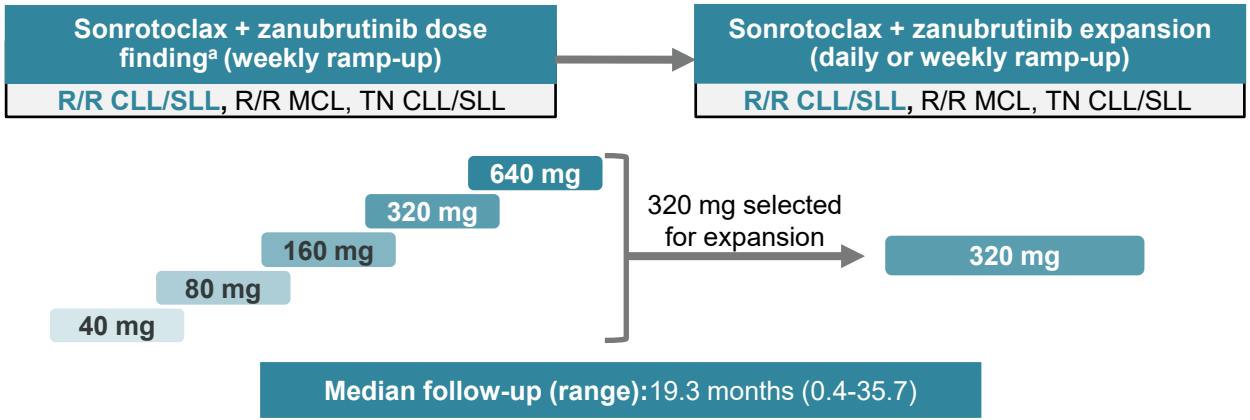
Introduction

- 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 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/SLL[5]
- 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)

1. Hillmen P, et al. *J Clin Oncol*. 2019;37(30):2722-2729. 2. Hu N, et al. AACR 2020. Abstract 3077. 3. Brukinsa. Prescribing information. BeiGene, Ltd; 2024.
4. Brukinsa. Summary of product characteristics. BeiGene, Ltd; 2021. 5. Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

BGB-11417-101 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
- 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 disease progression



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

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	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						
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.

TEAE Summary

- 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

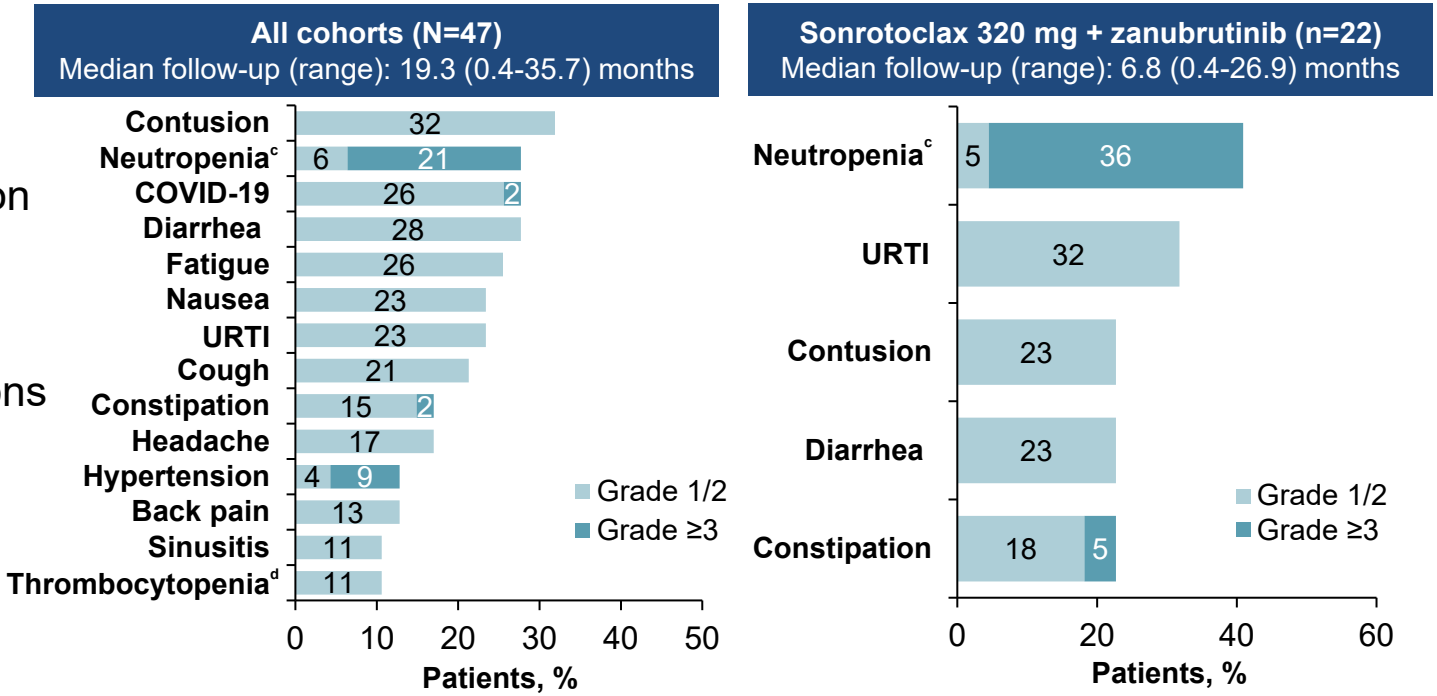
Patients, n (%)	Sonro 40 mg + zanu (n=4)	Sonro 80 mg + zanu (n=9)	Sonro 160 mg + zanu (n=6)	Sonro 320 mg + zanu (n=22)	Sonro 640 mg + zanu (n=6)	All (N=47)
Any TEAEs	4 (100)	9 (100)	6 (100)	20 (91)	5 (83)	44 (94)
Grade ≥3	1 (25)	5 (56)	3 (50)	13 (59)	2 (33)	24 (51)
Serious TEAEs	1 (25)	1 (11)	3 (50)	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)[c]	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

- No TLS
- No atrial fibrillation
- No febrile neutropenia
- No dose reductions due to diarrhea

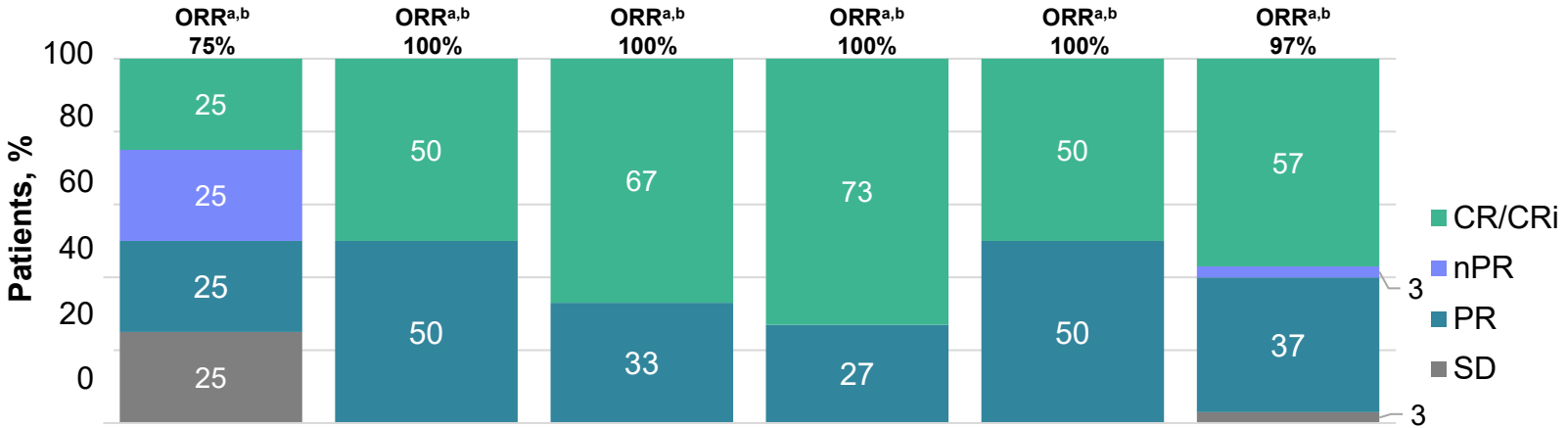
TEAEs in ≥5 patients of all patients and those treated at sonrotoclax RP2D of 320 mg[a,b]



[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*.

Sonrotoclax + Zanubrutinib Achieves Deep Responses Across All Dose Levels

- With a median study follow-up of 19.3 months, the ORR was 97%, with a 57% CR/CRi rate across all doses
  - 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

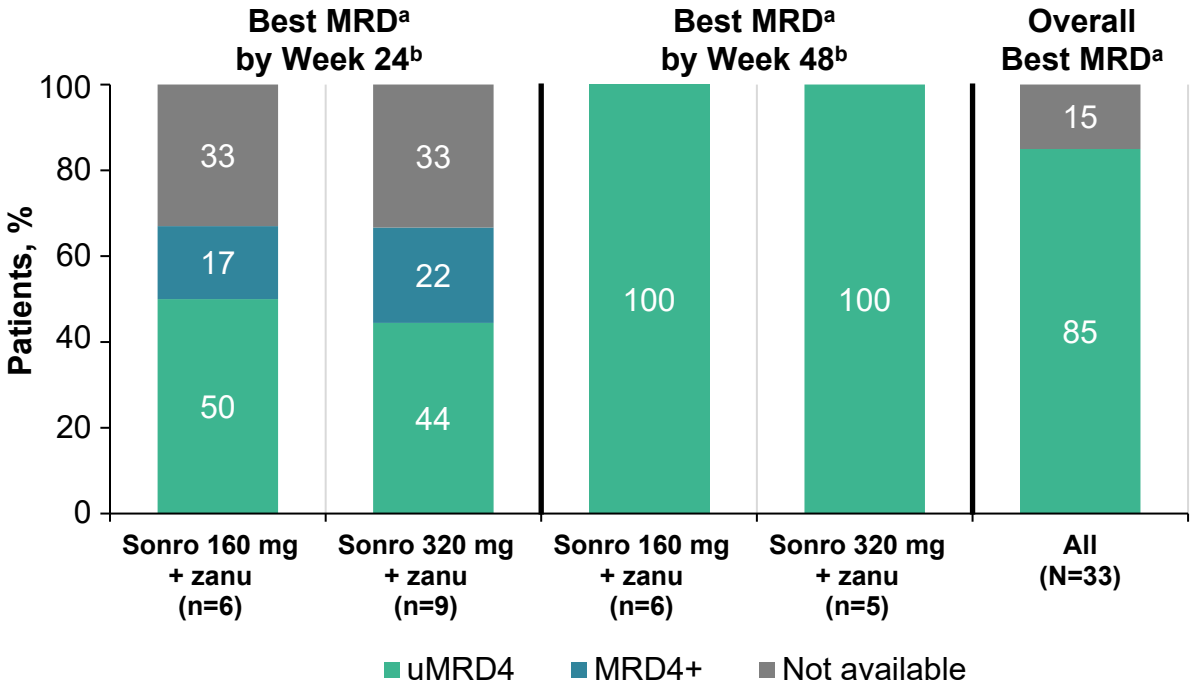


	Sonro 40 mg + zanu (n=4)	Sonro 80 mg + zanu (n=8)	Sonro 160 mg + zanu (n=6)	Sonro 320 mg[c,e] + zanu (n=11)	Sonro 640 mg + zanu (n=6)	Efficacy-evaluable population (N=35)
Follow-up time[d], median (range), months	34.0 (10.2-35.7)	27.7 (10.0-34.5)	29.2 (28.3-30.8)	6.8 (0.4-26.9)	18.1 (10.9-22.6)	19.3 (0.4-35.7)

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

Sonrotoclax + Zanubrutinib Achieved High Rates of uMRD in Peripheral Blood

- Of 33 MRD-evaluable patients, 28 (85%) had uMRD at time of data cutoff
- 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

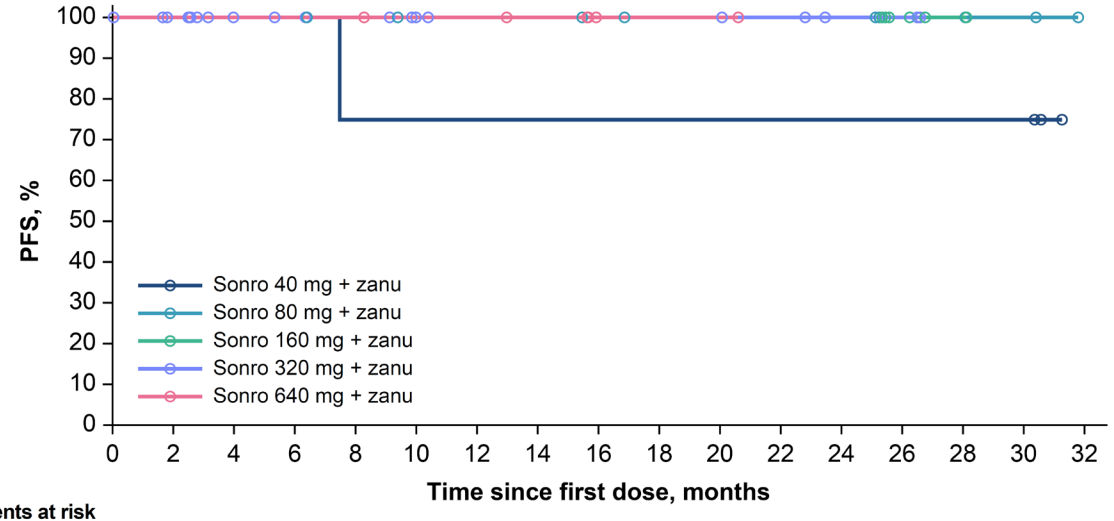


Data cutoff: February 18, 2024.

[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 $\geq 10^{-4}$ 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.

Progression-Free Survival

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



No. of patients at risk

Sonro 40 mg + zanu	4	4	4	4	4	4	4	4	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	1	0
Sonro 80 mg + zanu	9	9	9	9	9	9	8	8	8	7	7	7	7	7	7	6	5	5	5	5	5	5	5	3	3	3	2	2	1	0
Sonro 160 mg + zanu	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	3	1	1	0	0	0	0
Sonro 320 mg + zanu	22	19	17	13	11	11	10	9	9	9	6	5	5	5	5	5	5	5	5	5	4	4	3	2	2	2	0	0	0	0	0	0
Sonro 640 mg + zanu	6	6	6	6	6	6	6	6	6	5	5	5	5	4	4	4	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0

Data of Sonrotoclax + Zanubrutinib Demonstrates an Encouraging Safety and Efficacy Profile in Patients With R/R CLL

- 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 320mg
  - 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

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 Inizio company, and supported by BeiGene