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CONGRESSO NAZIONALE SIE
Società Italiana di Ematologia



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

Alessandra Tedeschi,¹ Stephan S. Opat,² Mary Ann Anderson,^{3,4} Emma Verner,^{5,6} Masa Lasica,⁷ Alejandro Arbelaez,⁸ Stephan Stilgenbauer,⁹ Peter Browett,¹⁰ Sophie Leitch,¹¹ Eva González 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,²⁰ Constantine S. Tam²²

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

MILANO, 23-25 Settembre 2024

MICO - Milano Convention Centre

Disclosures of Alessandra Tedeschi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie			X		X		
AstraZeneca			X				
BeiGene			X		X		
Janssen			X		X		
Lilly			X				

Introduction

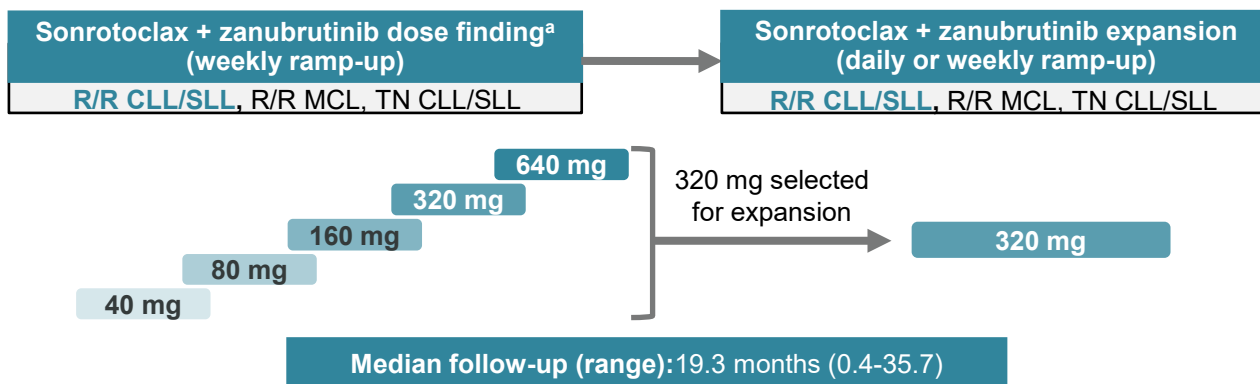
- CLL/SLL remains incurable as many treated patients experience relapse,¹ necessitating further treatment with novel agents
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax with a shorter half-life and no drug accumulation²
- Zanubrutinib is a next-generation BTK inhibitor approved globally for 5 indications, including CLL^{3,4}
 - Zanubrutinib has shown superior PFS and favorable 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)

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 (US). BeiGene, Ltd; 2024;

4. Brukinsa. Summary of product characteristics (EU). 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 \pm zanubrutinib, and \pm 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 PD



^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, 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.

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

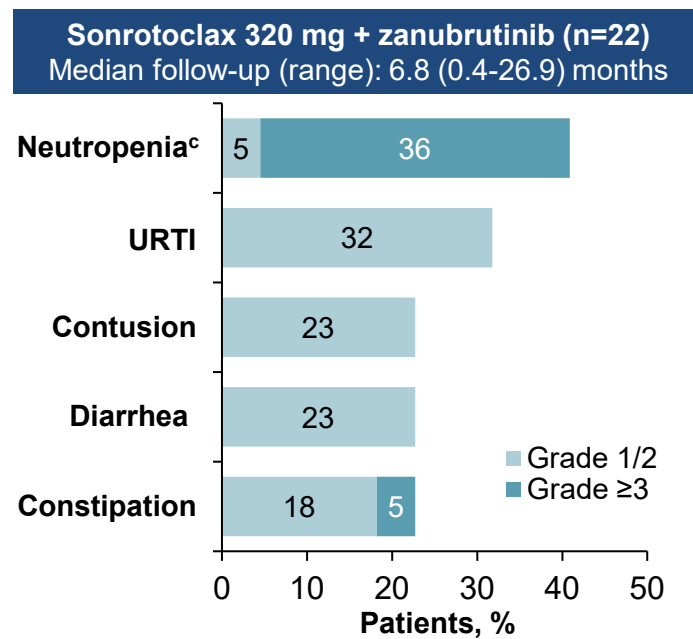
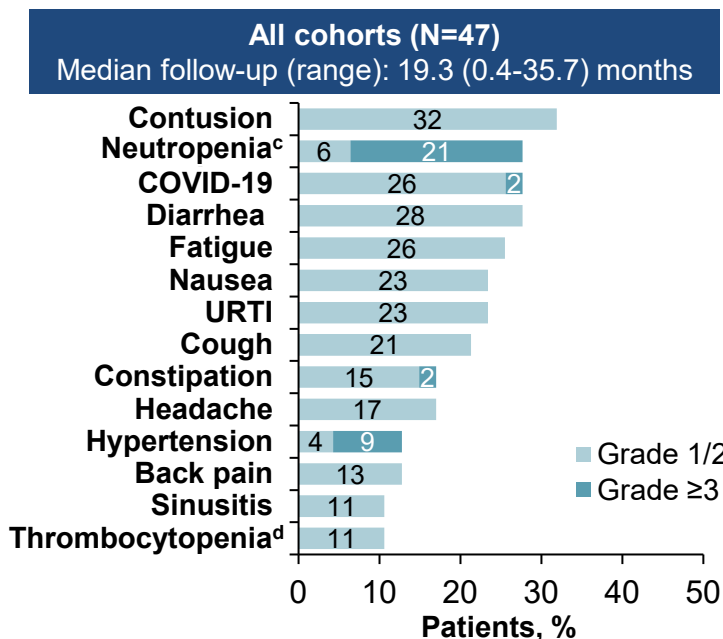
Patients, n (%)	Sonro 40 mg + zanu (n=4)	Sonro 80 mg + zanu (n=9)	Sonro 160 mg + zanu (n=6)	Sonro 320 mg + zanu (n=22)	Sonro 640 mg + zanu (n=6)	All (N=47)
Any TEAEs	4 (100)	9 (100)	6 (100)	20 (91)	5 (83)	44 (94)
Grade ≥3	1 (25)	5 (56)	3 (50)	13 (59)	2 (33)	24 (51)
Serious TEAEs	1 (25)	1 (11)	3 (50)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

TEAEs in ≥5 patients of all patients and those treated at sonrotoclox RP2D of 320 mg^{a,b}

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

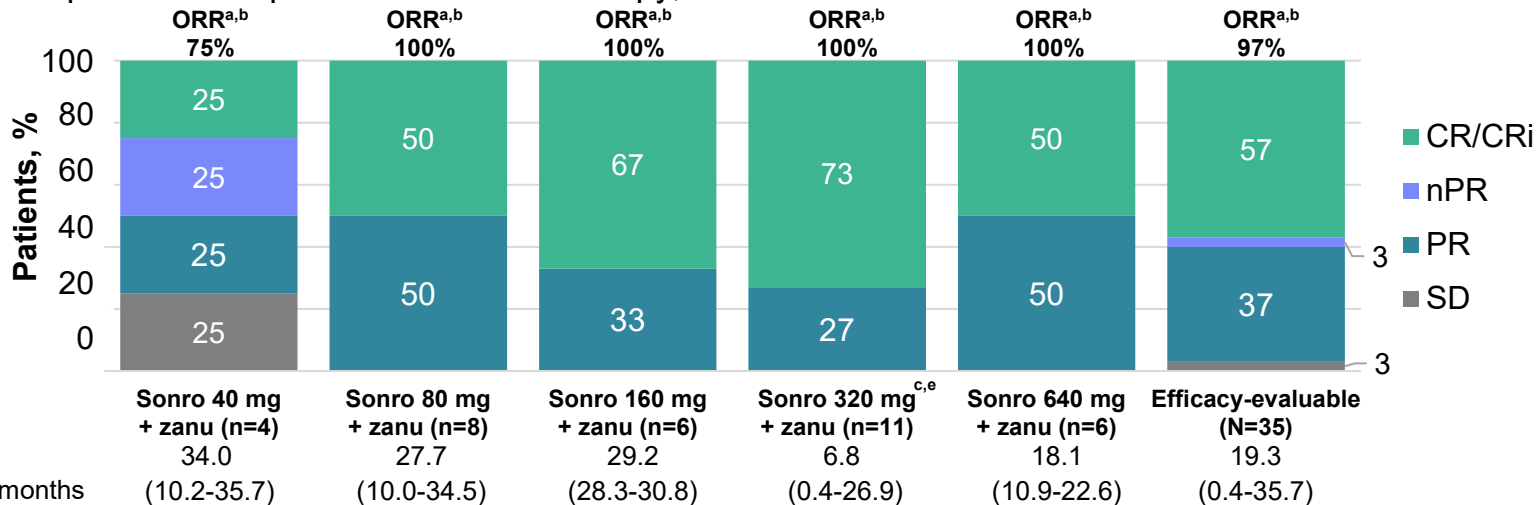


^a Grade is listed as worst grade experienced by patient on any drug. ^b Hematologic AEs were graded per iwCLL criteria; nonhematologic AEs were graded per CTCAE v5.0 criteria.

^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

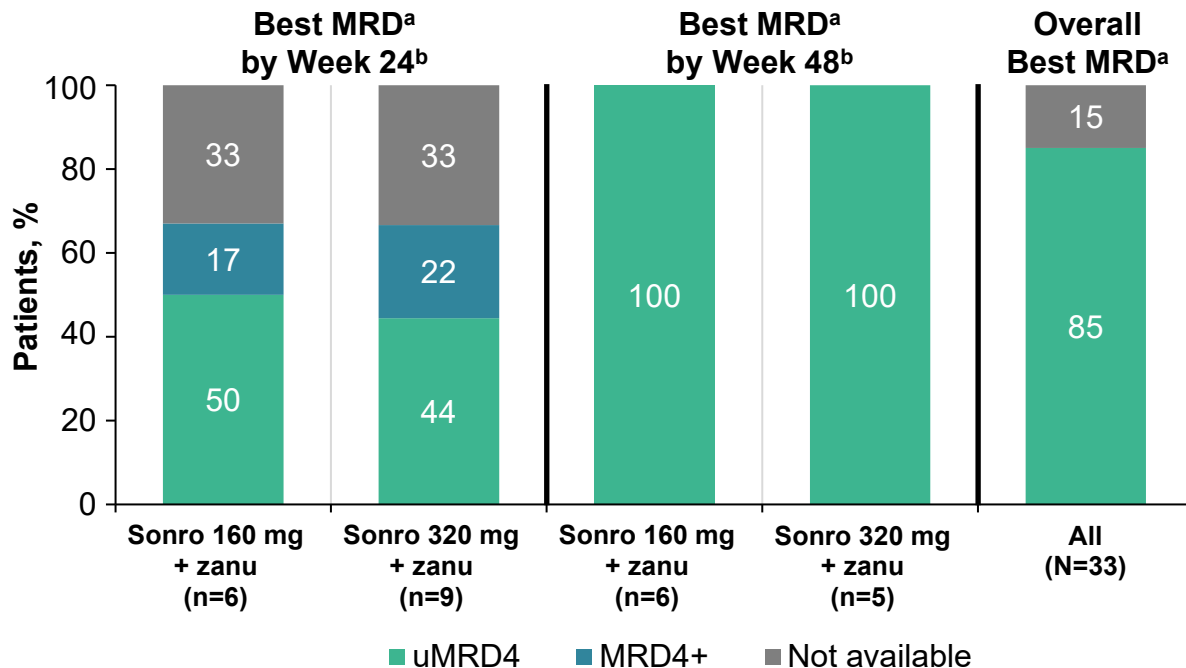


^a Responses were assessed per 2008 iwCLL criteria and percentage of response is based on number of patients who had at least 1 post-baseline tumor assessment after dosing sonrotoclax.

^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



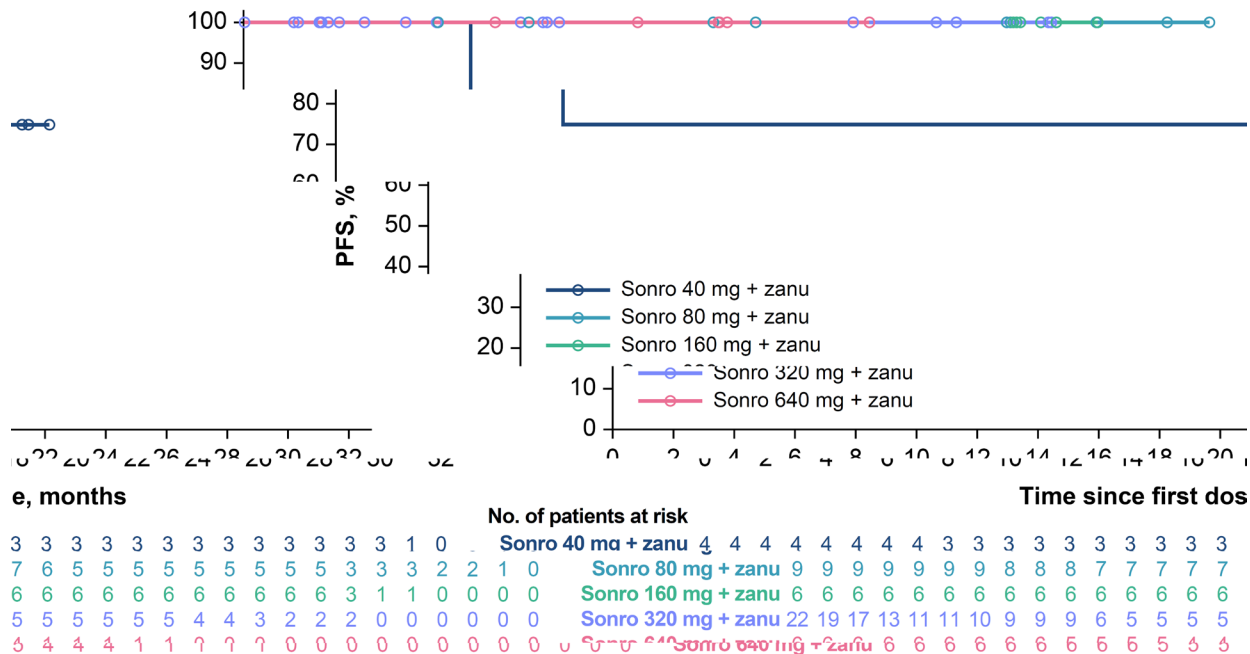
Data cutoff: February 18, 2024.

^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



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 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

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

Corresponding Author: Alessandra Tedeschi, alessandra.tedeschi@ospedaleniguarda.it