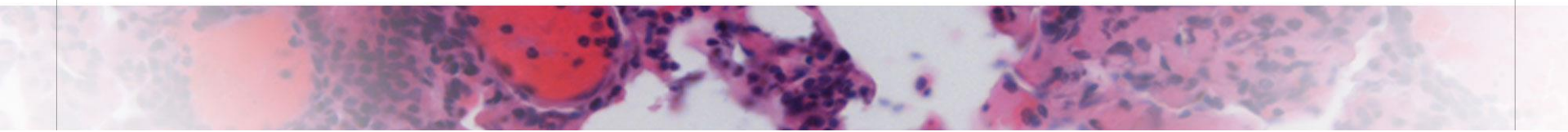
American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Combination Treatment with Sonrotoclax (BGB-11417), a Second-Generation BCL2 Inhibitor, and Zanubrutinib, a Bruton Tyrosine Kinase Inhibitor, is Well Tolerated and Achieves Deep Responses in Patients with Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Data From an Ongoing Phase 1/2 Study

Constantine S. Tam,[1,2] Mary Ann Anderson,[3,4] Masa Lasica,[5] Emma Verner,[6,7] Stephen Opat,[2,8] Shuo Ma,[9] Robert Weinkove,[10,11] Raul Cordoba,[12] Jacob Soumerai,[13] Paolo Ghia,[14] Sophie Leitch,[15] James Hilger,[16] Yiqian Fang,[16] David Simpson,[16] Haiyi Guo,[16] Chan Y. Cheah[17-19]

[1]Alfred Hospital, Melbourne, VIC, Australia; [2]Monash University, Clayton, VIC, Australia; [3]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [4]Division of Blood Cells and Blood Cancer, The Walter and Eliza Hall Institute, Parkville, VIC, Australia; [5]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [6]Concord Repatriation General Hospital, Concord, NSW, Australia; [7]University of Sydney, Sydney, NSW, Australia; [8]Monash Health, Clayton, VIC, Australia; [9]Northwestern University Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA; [10]Te Rerenga Ora Wellington Blood & Cancer Centre, Te Whatu Ora Health New Zealand Capital, Coast & Hutt Valley, Wellington, New Zealand; [11]Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, Wellington, New Zealand; [12]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [13]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [14]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [15]Te Whatu Ora Health New Zealand Waitamata, Auckland, New Zealand; [16]BeiGene (Shanghai) Co., Ltd., Shanghai, China and BeiGene USA, Inc., San Mateo, CA, USA; [17]Department of Haematology, Sir Charles Gairdner Hospital and PathWest Laboratory Medicine, Nedlands, WA, Australia; [18]Medical School, University of Western Australia, Crawley, WA, Australia; [19]Linear Clinical Research, Nedlands, WA, Australia

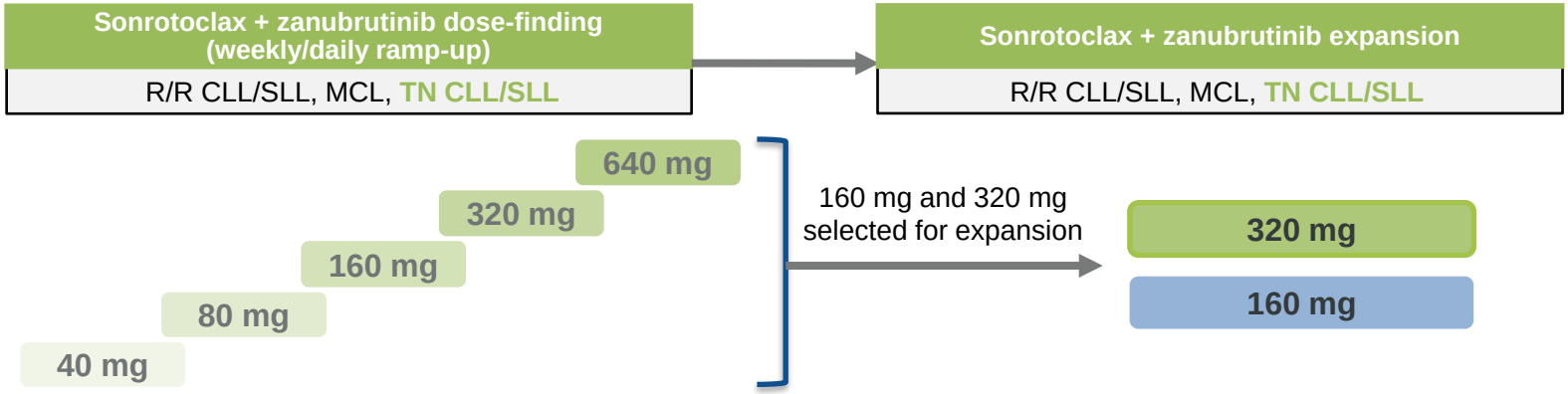
Background

- Sonrotoclax is a BH3 mimetic that binds and inhibits BCL2
  - >10-fold potency compared with venetoclax[1] and better in vitro activity against BCL2 mutations, including BCL2 G101V
  - Demonstrated high selectivity
  - Short half-life (4 hours)
- The combination of BCL2 and BTK inhibitors has shown synergistic activity in preclinical CLL models[2-5]
- Ibrutinib with venetoclax in patients with CLL/SLL is effective; however, toxicities can limit use[6]
- Zanubrutinib is highly effective in patients with TN and RR CLL/SLL including those with high-risk diseases[7,8]
  - Zanubrutinib demonstrated a superior efficacy and safety profile, including less cardiovascular toxicity than ibrutinib in R/R CLL/SLL[8]
- Here, we report preliminary results of the BGB-11417-101 trial (NCT04277637) in patients with TN CLL/SLL treated with sonrotoclax in combination with zanubrutinib

1. Hu N, et al. AACR 2020. Abstract 3077; 2. Soumerai JD, et al. *Lancet Haematol*. 2021;8(12):e879-e890; 3. Hillmen P, et al. *J Clin Oncol*. 2019;37(30):2722-2729; 4. Jain N, et al. *N Engl J Med*. 2019;380(22):2095-2103; 5. Wierda WG, et al. *J Clin Oncol*. 2021;39(34):3853-3865; 6. Kater AP, et al. *NEJM Evidence*. 2022;1(7); 7. Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043; 8. Brown JR, et al. *Clin Lymphoma Myeloma Leuk*. 2022;22:S266.

Study Design and Methods

- BGB-11417-101 is a phase 1/2 study evaluating sonrotoclax as monotherapy, in combination with zanubrutinib, and in combination with obinutuzumab± zanubrutinib in patients with B-cell malignancies
- Main study objectives (TN CLL/SLL cohorts): determine safety and tolerability and define the RP2D of sonrotoclax when given in combination with zanubrutinib (160 mg BID or 320 mg QD)



- 8 to 12 weeks of zanubrutinib monotherapy was given prior to sonrotoclax dosing (12 weeks if high tumor burden)
- Sonrotoclax was dosed orally, once daily, using a weekly or daily ramp-up schedule to reach the target dose

Baseline Characteristics

Characteristics	Sonrotoclax 160 mg + zanu (n=51)	Sonrotoclax 320 mg + zanu (n=56)	All Patients (N=107)
Study follow up time, median (range), months	7.2 (0.3-21.1)	9.8 (0.5-17.4)	9.7 (0.3-21.1)
Age, median (range), years	63 (38-82)	61 (34-84)	62 (34-84)
≥65 years, n (%)	20 (39)	19 (34)	39 (36)
≥75 years, n (%)	4 (8)	7 (13)	11 (10)
Sex, n (%)			
Male	37 (73)	44 (79)	81 (76)
Disease type, n (%)			
CLL	49 (96)	52 (93)	101 (94)
SLL	2 (4)	4 (7)	6 (6)
Risk status, n/tested (%)[a]			
del(17p)	6/49 (12)	6/54 (11)	12/103 (12)
del(17p) and/or *TP53*^{mut}	12/50 (24)	15/55 (27)	27/105 (26)
IGHV status, n/tested (%)			
Unmutated	33/47 (70)	28/51 (55)	61/98 (62)
Tumor bulk at baseline, n (%)			
High[b]	20 (39)	14 (25)	34 (32)
Not High	31 (61)	42 (75)	73 (68)

Data cutoff: August 15, 2023.

[a]*TP53* mutations defined as >10% VAF. [b]Nodes ≥10 cm or nodes >5 cm and ALC >25 × 10^9/L.

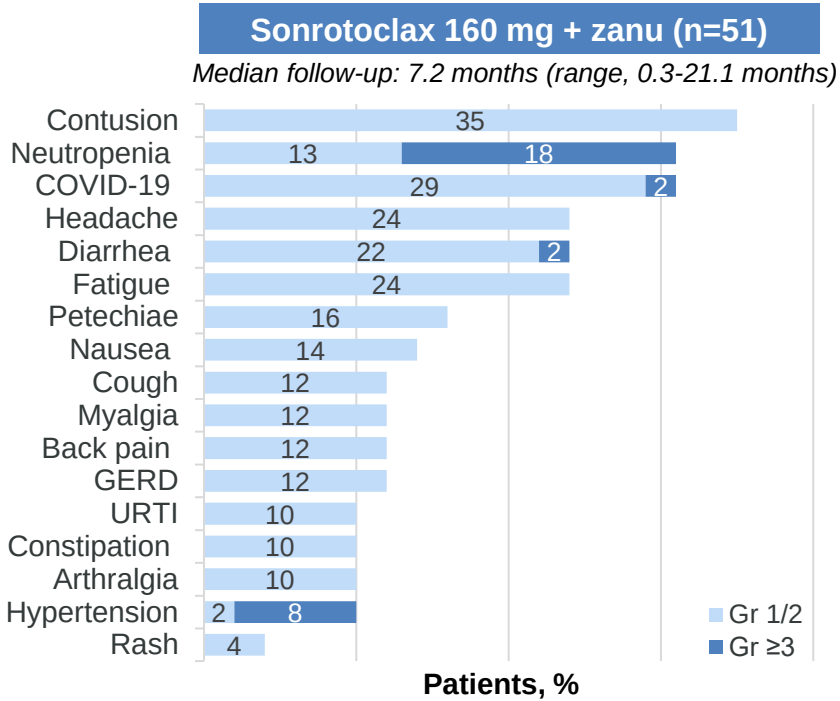
Dose Modification and AE Summary

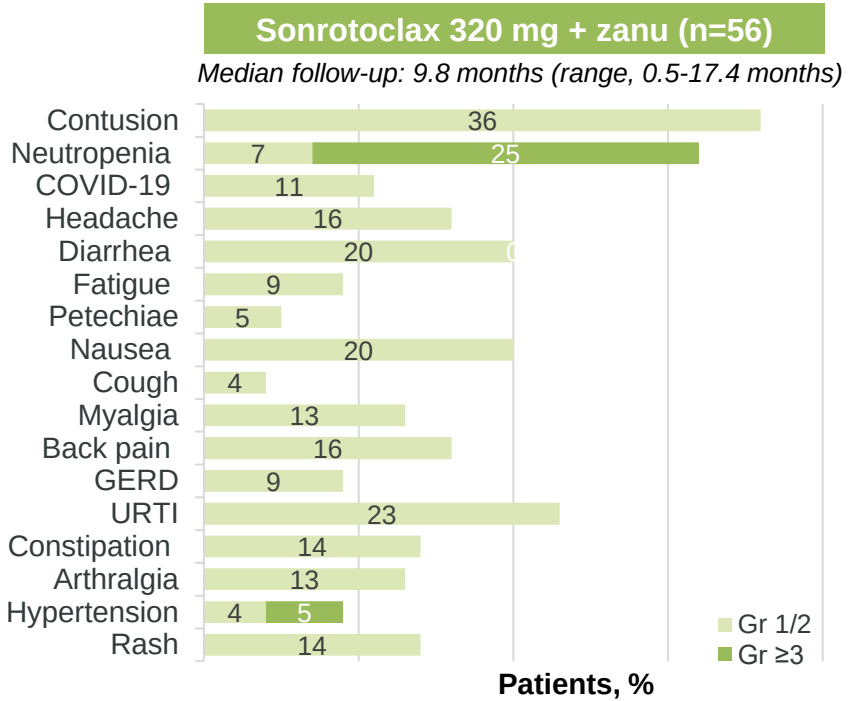
	Sonrotoclax 160 mg + zanu (n=51)	Sonrotoclax 320 mg + zanu (n=56)	All Patients (N=107)
Any AEs, n (%)	47 (92.2)	49 (87.5)	96 (89.7)
Grade ≥3	22 (43.1)	21 (37.5)	43 (40.2)
Serious AEs	7 (13.7)	8 (14.3)	15 (14.0)
Leading to death	0	0	0
Leading to dose reduction of zanubrutinib	1 (2.0)	2 (3.6)	3 (2.8)
Leading to discontinuation of zanubrutinib[a]	1 (2.0)	0	1 (0.9)
Treated with sonrotoclax, n (%)	41 (80.4)	53 (94.6)	94 (87.9)
Leading to hold of sonrotoclax	11 (26.8)	10 (18.9)	21 (22.3)
Leading to dose reduction of sonrotoclax	2 (4.9)	3 (5.7)	5 (5.3)
Leading to discontinuation of sonrotoclax[a]	1 (2.4)	0	1 (1.1)

- Sonrotoclax in combination with zanubrutinib is well tolerated and generally favorable, with very low rates of treatment discontinuation and dose reductions

[a]One patient stopped both sonrotoclax and zanubrutinib due to fungal infection.

Most Frequent AEs (Incidence ≥5 Patients)[a,b]





- AEs observed with sonrotoclax + zanubrutinib combination therapy were mostly grades 1 and 2

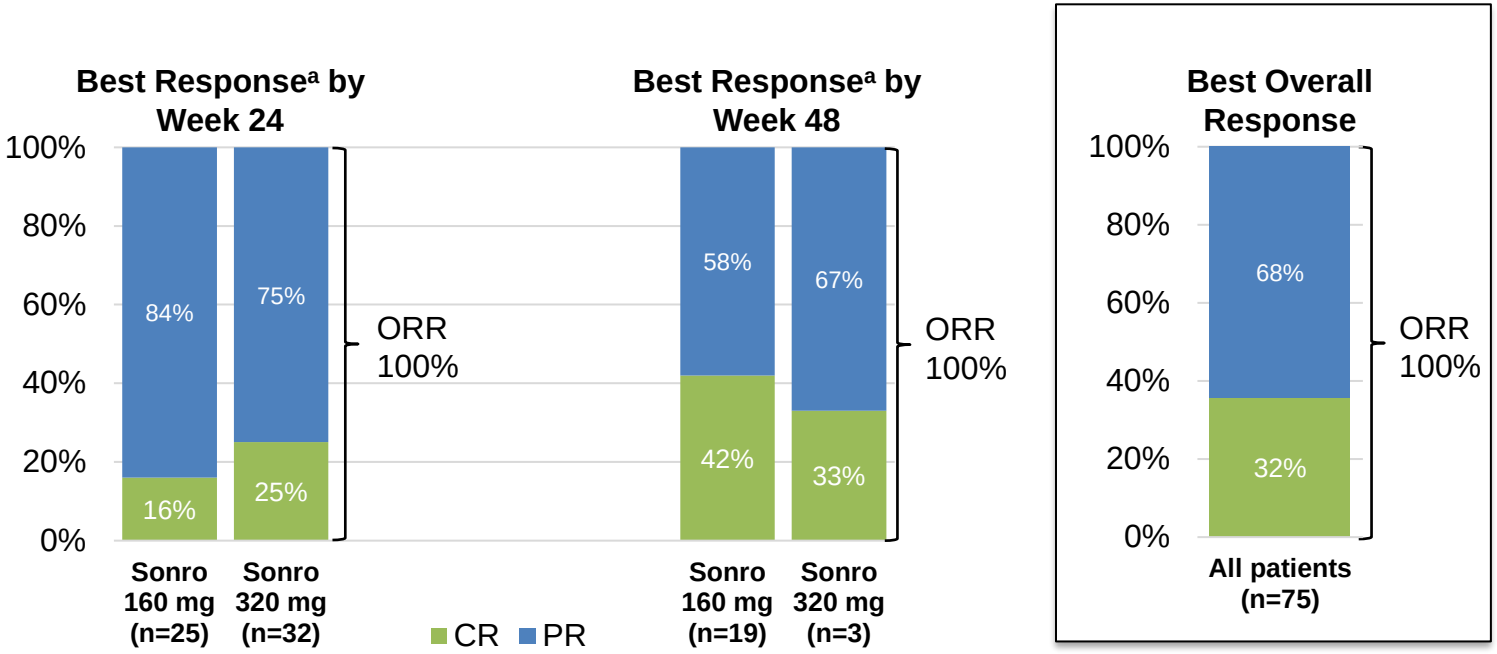
[a]Grade is listed as worst grade experienced by patient on any drug. [b]Hematologic AEs were graded per iwCLL criteria; nonhematologic AEs were graded per CTCAE v5.0 criteria.

TEAEs of Interest

TLS[a]	No clinical or laboratory TLS was observed with weekly or daily ramp-up
GI toxicity[b]	Diarrhea events were mostly Grade 1; no dose reductions occurred
Atrial fibrillation	No atrial fibrillation was observed
Neutropenia	Most frequent AE (and Grade ≥3 AE); 1 dose reduction/no dose holds, 18 patients (17%) used G-CSF[c]
Febrile neutropenia	Observed in 2 patients (2%) assigned to the 160 mg dose level; events resolved without sequelae
Infections	Low rate of Grade ≥3 infections (8%); pneumonia (n=4) was the only Grade ≥3 infection in more than 1 patient

[a]TLS, tumor lysis syndrome, defined by Howard criteria. [b]One patient experienced multiple episodes of Grade 2 diarrhea so ramp-up was paused at 80 mg, they subsequently increased to 160 mg. [c]Includes all patients reporting G-CSF use during treatment, regardless of whether it was used for neutropenia or prophylaxis. G-CSF was used in 7 patients in the 160 mg cohort (14%) and 11 patients in the 320 mg cohort (20%). The median duration was 10 days.

Overall Response Rate

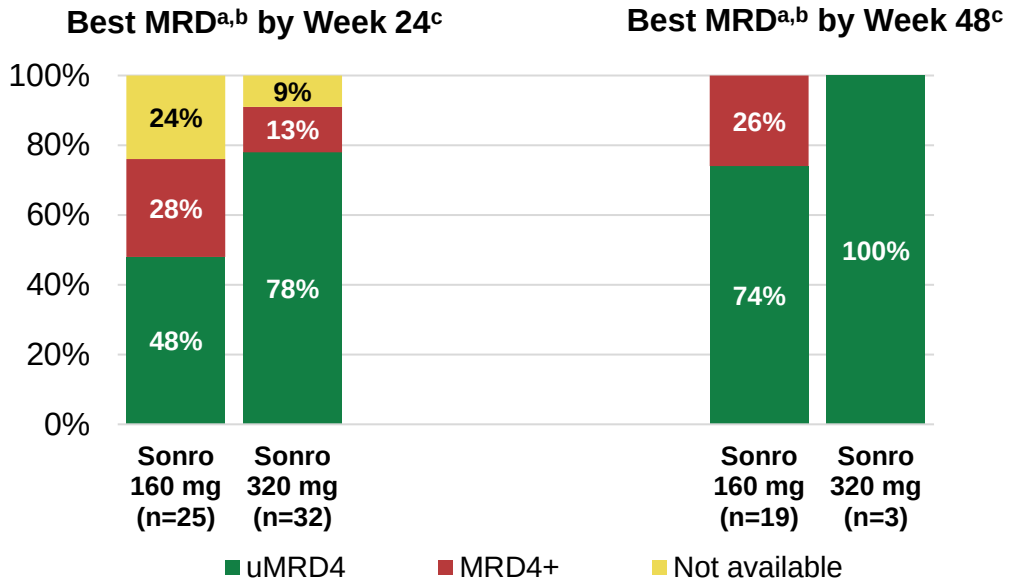


Response rates improved with time

[a]Percentage of response is based on number of patients who have reached the assessment at 24 or 48 weeks after completion of ramp-up, following zanubrutinib monotherapy and sonrotoclax ramp-up to target dose.

Minimal Residual Disease in Peripheral Blood

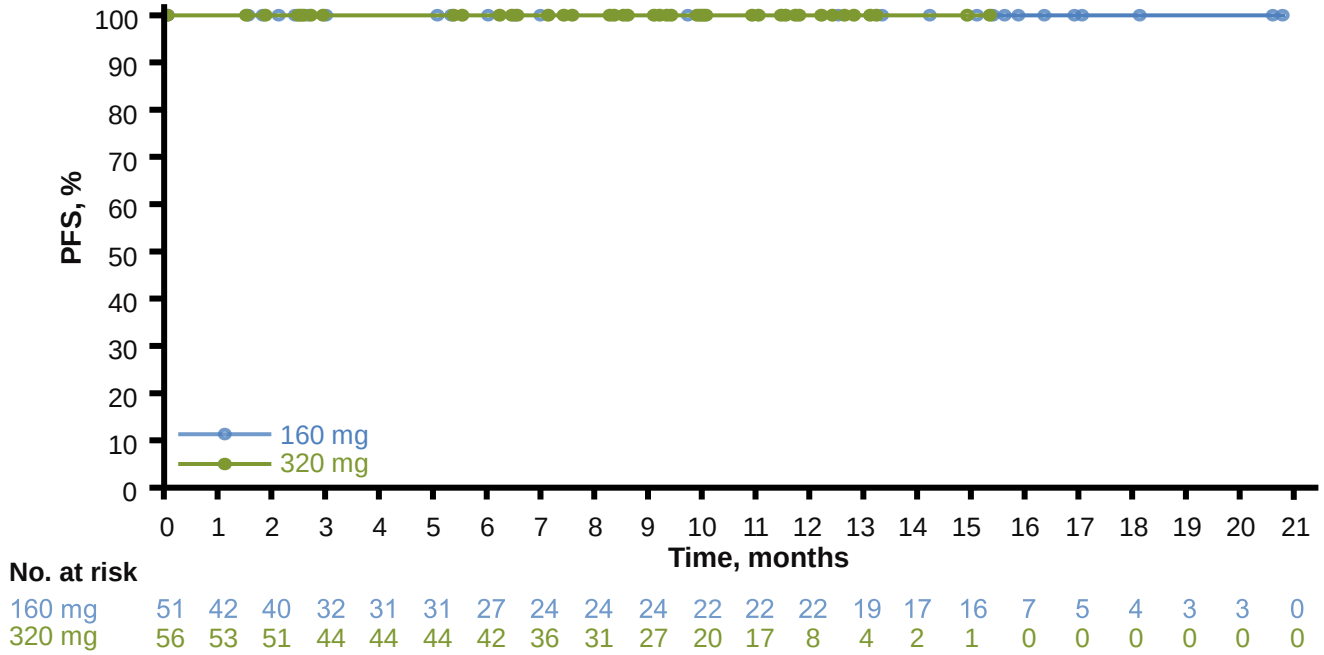
- High uMRD achieved at both dose levels
- Trend for higher uMRD rates with 320 mg
- Evidence of deepening response over time



[a]MRD was measured by ERIC flow cytometry with 10^{-4} sensitivity. uMRD4 is defined as the number of CLL cells of total nucleated cells $<10^{-4}$. MRD4+ is defined as the number of CLL cells of total nucleated cells $>10^{-4}$; [b]MRD is best reported within a 2-week window following the Week 24 Day 1 and Week 48 Day 1 MRD assessment timepoints, respectively; [c]Week 24 or 48 represents 24 or 48 weeks at target dose, following zanubrutinib monotherapy and sonrotoclax ramp-up to target dose.

Progression-Free Survival

- At a median follow-up of 9.7 months, no patient has experienced disease progression or died at either sonrotoclax dose level



Conclusions

- Sonrotoclax 160 or 320 mg in combination with zanubrutinib 320 mg QD was safe and well tolerated
  - 106/107 of patients remain on treatment
  - No TLS and no cardiac toxicity were observed; low rates of GI AEs (predominantly Grade 1)
  - The most commonly reported grade ≥3 AE was neutropenia which was mostly transitory, and not requiring dose modifications or interruptions
- Efficacy was promising in this all-comer TN CLL/SLL population
  - ORR was 100%
  - High blood MRD negativity by Week 24, with deepening response by Week 48 of combination therapy
  - No PFS events were observed as of the data cutoff
- Based on these data, sonrotoclax 320 mg was selected for the phase 3 study in combination with zanubrutinib in patients with TN CLL

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 (BeiGene) for their work on the MRD analyses and Sheel Patel (BeiGene) for assistance in development of this presentation
- This study was sponsored by BeiGene, Ltd
- Editorial assistance was provided by Nucleus Global, an Inizio Company, and supported by BeiGene

Corresponding Author: Constantine Tam, constantine.tam@alfred.org.au