A Phase 1 Study With the Novel B-cell Lymphoma 2 Inhibitor Sonrotoclax (BGB-11417) as Monotherapy or in Combination With Zanubrutinib in Patients With CLL/SLL: Preliminary Data

Damien Roos-Weil[1], Chan Y. Cheah[2-4], Constantine S. Tam[5,6], Masa Lasica[7], Emma Verner[8,9], Peter J. Browett[10], Mary Ann Anderson[11,12], James Hilger[13], Yiqian Fang[13], David Simpson[13], Stephen Opat[7,14]

[1]Pitié-Salpêtrière Hospital, Sorbonne University, Paris, France; [2]Department of Haematology, Sir Charles Gairdner Hospital and PathWest Laboratory Medicine, Nedlands, WA, Australia; [3]Medical School, University of Western Australia, Crawley, WA, Australia; [4]Linear Clinical Research, Nedlands, WA, Australia; [5]Alfred Hospital, Melbourne, VIC, Australia; [6]Monash University, Clayton, VIC, Australia; [7]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [8]Concord Repatriation General Hospital, Concord, NSW, Australia; [9]University of Sydney, Sydney, NSW, Australia; [10]Department of Haematology, Auckland City Hospital, Auckland, New Zealand; [11]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [12]Division of Blood Cells and Blood Cancer, The Walter and Eliza Hall Institute, Parkville, VIC, Australia; [13]BeiGene (Shanghai) Co., Ltd., Shanghai, China and BeiGene USA, Inc., San Mateo, CA, USA; [14]Monash Health, Clayton, VIC, Australia

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Introduction

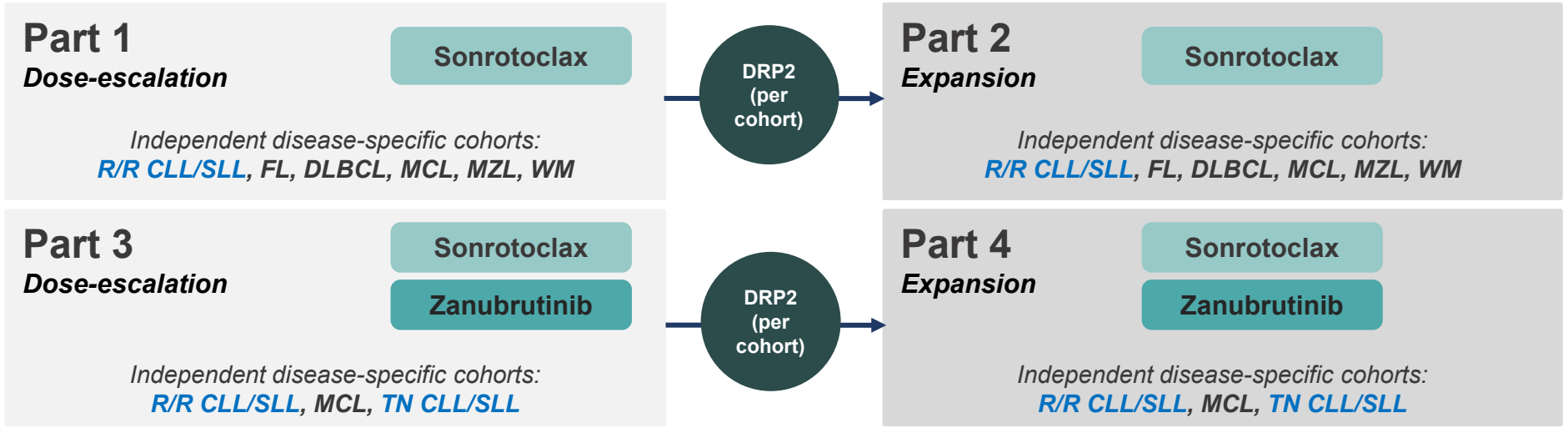
- BCL2 inhibition is an established mechanism for treating B-cell malignancies such as CLL/SLL[1-2]
- Sonrotoclax (BGB-11417) has shown more potent and selective BCL2 inhibition and better activity against BCL2 mutations than venetoclax in vitro[2]
- The combination of BCL2 and BTK inhibitors has potent activity in CLL and MCL[3-6]
- Ibrutinib with venetoclax has shown efficacy as a first-line treatment in a phase 3 trial in patients with CLL/SLL; however, toxicities can limit use[7]
  - A more tolerable BTK inhibitor + BCL2 inhibitor combination is needed
- Zanubrutinib has demonstrated superior PFS and safety, especially cardiovascular, in a head-to-head study vs ibrutinib in patients with R/R CLL[8]
- Here, we present the preliminary data from a phase 1 study with sonrotoclax as monotherapy or combination with zanubrutinib in patients with CLL/SLL

BCL2, B-cell lymphoma 2; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; SLL, small lymphocytic lymphoma.

1. Kapoor et al. *Cell Death Dis*. 2020;11(11):941; 2. Hu et al. AACR 2020. Abstract 3077; 3. Soumerai et al. *Lancet Haematol*. 2021;8(12):e879-e890; 4. Hillmen et al. *J Clin Oncol*. 2019;37(30):2722-2729; 5. Jain et al. *N Engl J Med*. 2019;380(22):2095-2103; 6. Wierda et al. *J Clin Oncol*. 2021;39(34):3853-3865; 7. Kater et al. *NEJM Evidence*. 2022;1(7); 8. Brown et al. *Clin Lymphoma Myeloma Leuk*. 2022;22:S266.

Study Design

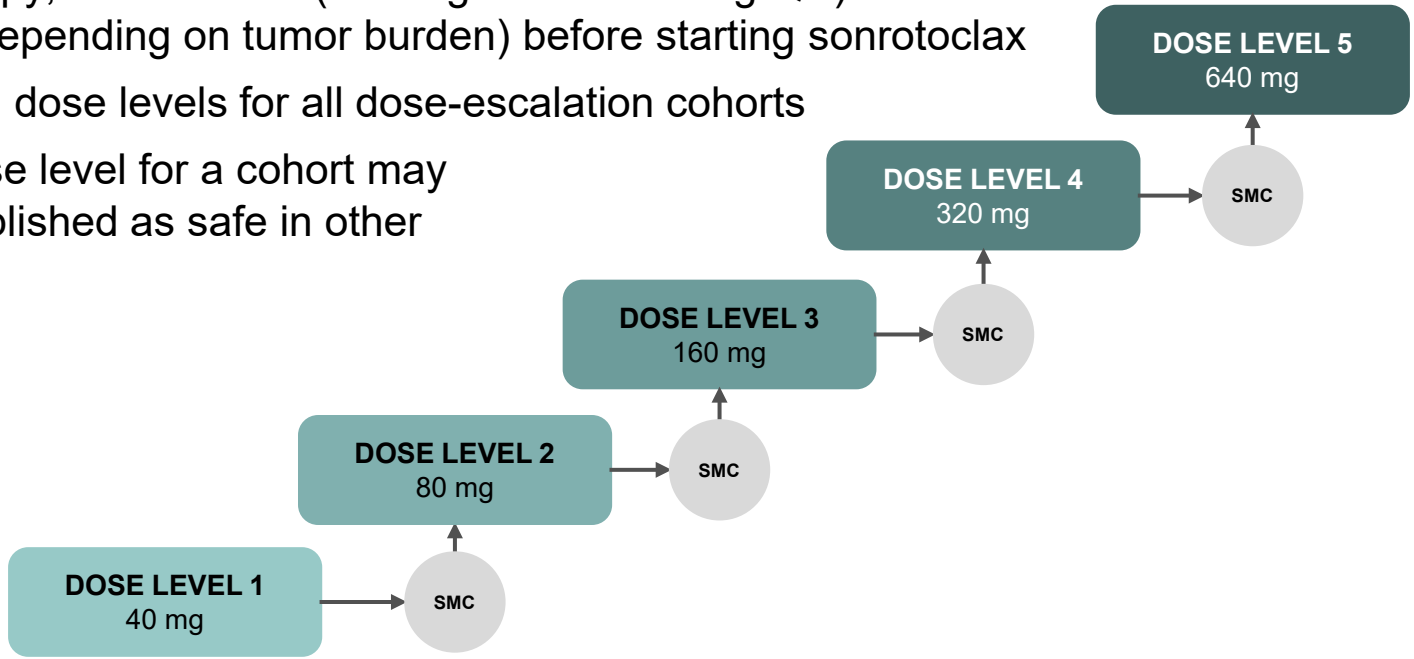
- BGB-11417-101 is a first-in-human, phase 1, open-label, multicenter, dose escalation and expansion study in patients with B-cell malignancies (NCT04277637)
- **Blue:** CLL/SLL cohort data focused on in this presentation



CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; RP2D, recommended phase 2 dose; SLL, small lymphocytic lymphoma; TN, treatment-naive; WM, Waldenström macroglobulinemia.

Dosing and Dose Escalation

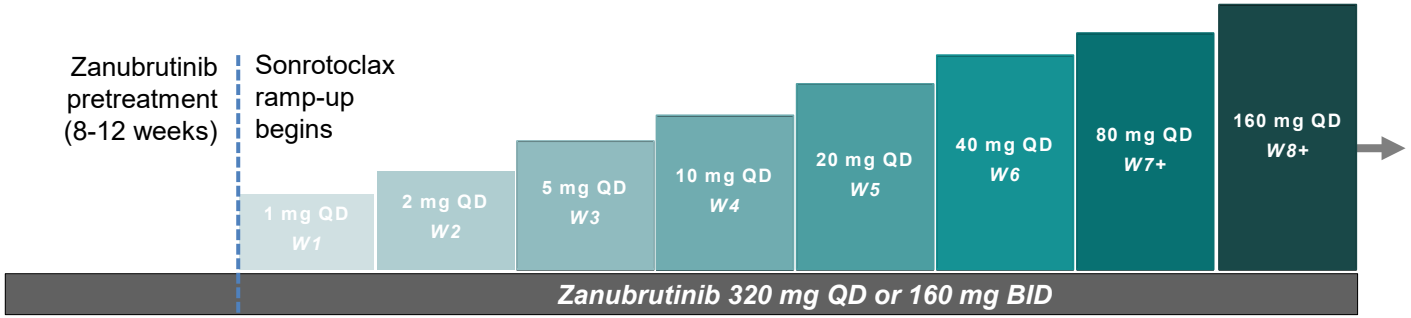
- Sonrotoclax was dosed QD ≤30 minutes after a low-fat meal
- For combination therapy, zanubrutinib (160 mg BID or 320 mg QD) started 8-12 weeks (depending on tumor burden) before starting sonrotoclax
- Five potential planned dose levels for all dose-escalation cohorts
  - Starting target dose level for a cohort may be >40 mg if established as safe in other cohorts per SMC[a]



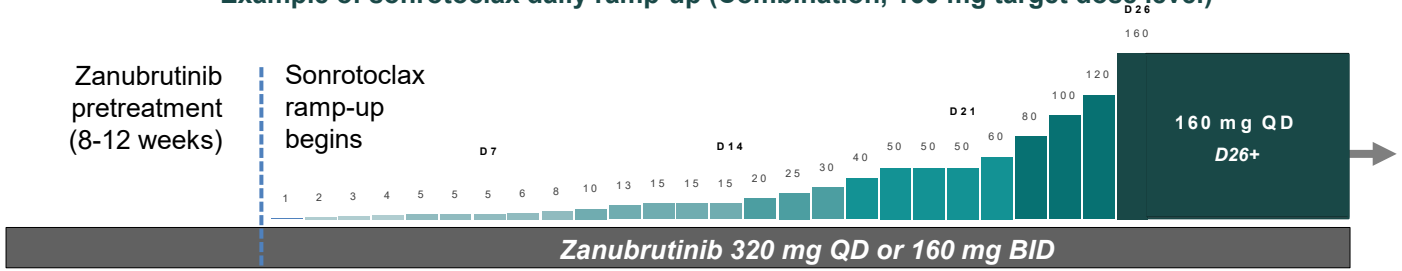
[a] SMC review of dose-level cohort data before dose escalation.
SMC, safety monitoring committee.

Dose Ramp-up Schedules

Example of sonrotoclax weekly ramp-up (Combination, 160 mg target dose level)



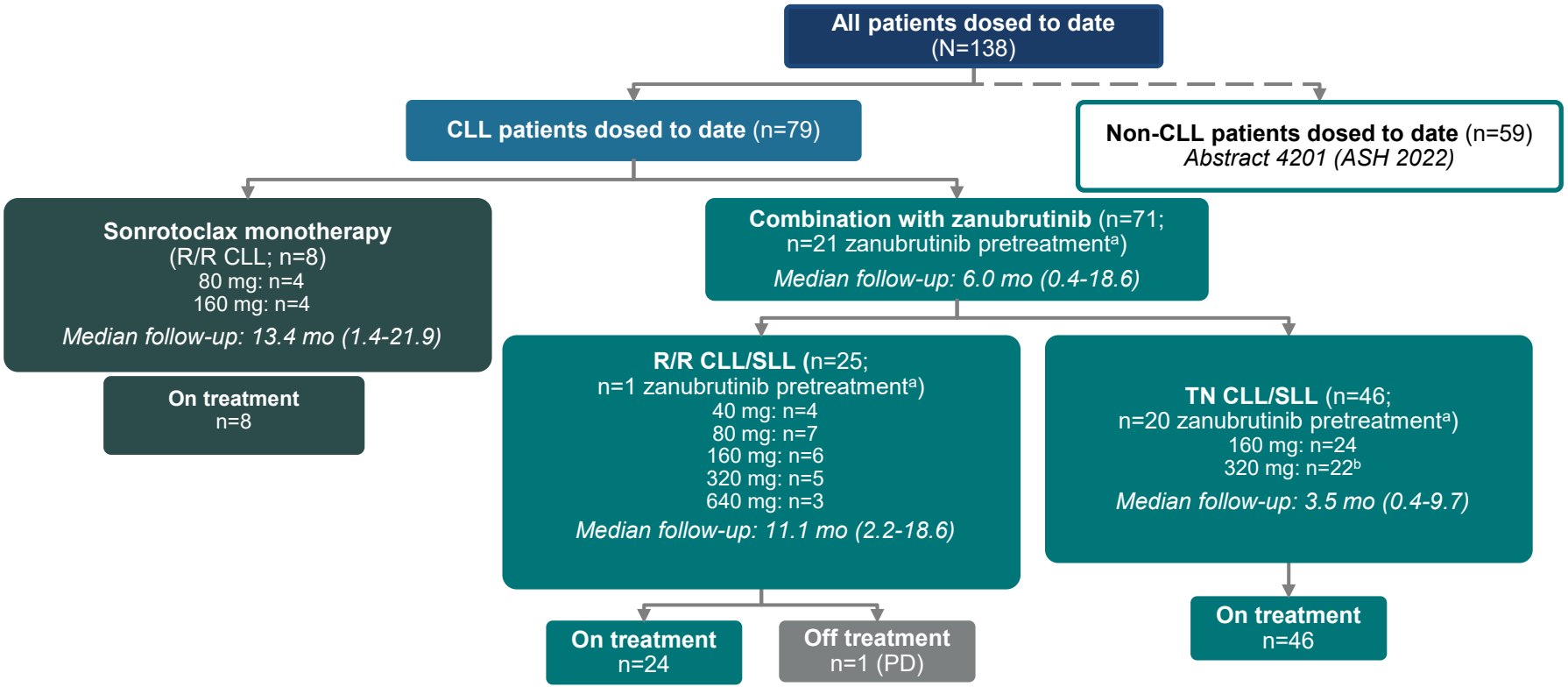
Example of sonrotoclax daily ramp-up (Combination, 160 mg target dose level)



- TLS prophylaxis included hydration and started 24-48 hours prior to first dose
- Allopurinol started 2-3 days prior to first dose and rasburicase started as indicated
- Hospitalization for observation was initially required for each new ramp-up dose level for first 3 dose levels, but the requirement has been removed per SMC

SMC, safety monitoring committee; TLS, tumor lysis syndrome; W, week.

Patient Disposition



Data cutoff date: 01 Sep 2022. [a] Patients who are still in the zanubrutinib pretreatment phase and have not yet received sonrotoclax. [b] All patients were assigned to a weekly ramp-up schedule except for n=4 TN patients (320 mg dose level). CLL, chronic lymphocytic leukemia; mo, months; SLL, small lymphocytic lymphoma; TN, treatment-naive.

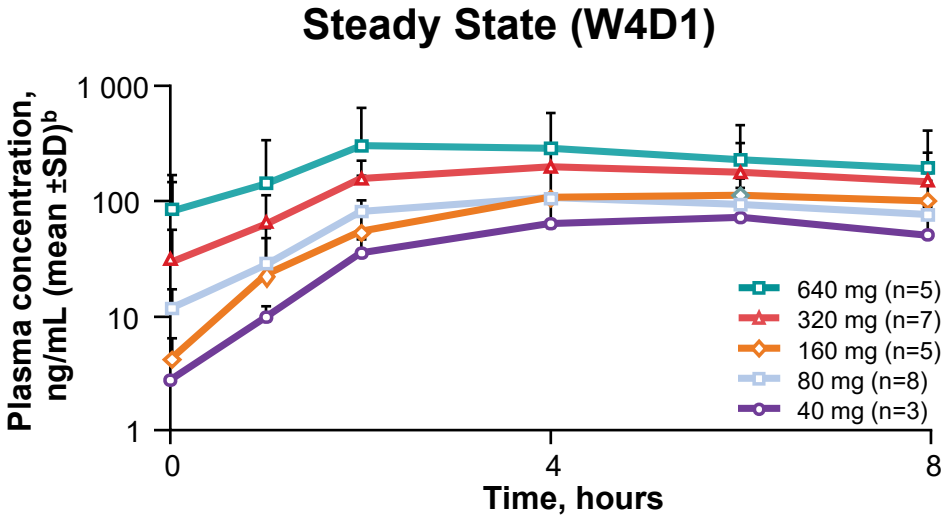
Patient Characteristics

Characteristic	Sonrotoclax monotherapy (n=8)	Sonrotoclax + zanubrutinib (n=71)	All patients (N=79)
Median age, (range), years	68.5 (55-84)	61 (35-84)	62 (35-84)
Sex, n (%)			
Male	6 (75)	56 (78.9)	62 (78.5)
Female	2 (25)	15 (21.1)	17 (21.5)
ECOG PS, n (%)			
0	3 (37.5)	49 (69)	52 (65.8)
1	5 (62.5)	21 (29.6)	26 (32.9)
2	0	1 (1.4)	1 (1.3)
Disease type, n (%)			
CLL	8 (100)	70 (99)	78 (99)
SLL	0	1 (1)	1 (1)
R/R, n (%)	8 (100)	25 (35.2)	33 (41.8)
No. of prior lines of therapy, median (range)	2 (1-3)	1 (1-2)	1 (1-3)
Time from end of most recent systemic therapy to first dose, median (range), months	0.4 (0.0-10.2)	57.0 (1.6-194.4)	45.4 (0.0-194.4)
TN, n (%)	0	46 (64.8)	46 (58.2)
Risk status, n (%)			
del(17p)	2 (25)	11 (15.5)	13 (16.5)
TP53^{mut}	3 (37.5)	15 (21.1)	18 (22.8)

CLL, chronic lymphocytic leukemia; del(17p), deletion in chromosome 17p; ECOG PS, Eastern Cooperative Oncology Group Performance Status; mut, mutant; SLL, small lymphocytic lymphoma; TN, treatment-naive; *TP53*, tumor protein 53.

Steady State Pharmacokinetics[a]

- Preliminary steady state PK data from patients with NHL or CLL who received sonrotoclax monotherapy at 40-640 mg target doses QD for 3 weeks
  - Dose-dependent PK from 40-640 mg
  - Fast absorption (median T_{max} ~4 hours)
  - Short half-life (median $T_{½}$ ~5 hours)
  - No significant accumulation at steady state
  - Similar PK with and without zanubrutinib (data not shown)



[a] PK data were pooled from all study cohorts, not just CLL. [b] Mean ±SD steady state sonrotoclax plasma concentration profile for 40-640 mg QD in patients with NHL and CLL who received sonrotoclax monotherapy (combination PK not shown here).
CLL, chronic lymphocytic leukemia; PK, pharmacokinetics; SD, standard deviation; $T_{½}$, half-life; T_{max}, maximum time; W, week.

Summary of AEs and DLTs

- Only 1 DLT of febrile neutropenia noted among patients with CLL with sonrotoclax monotherapy at 80 mg; no DLTs were observed to date with the combination therapy at any dose level
- Toxicity does not seem dose dependent
- These AEs are consistent with sonrotoclax NHL data,[1] which tested through 640 mg with no MTD reached

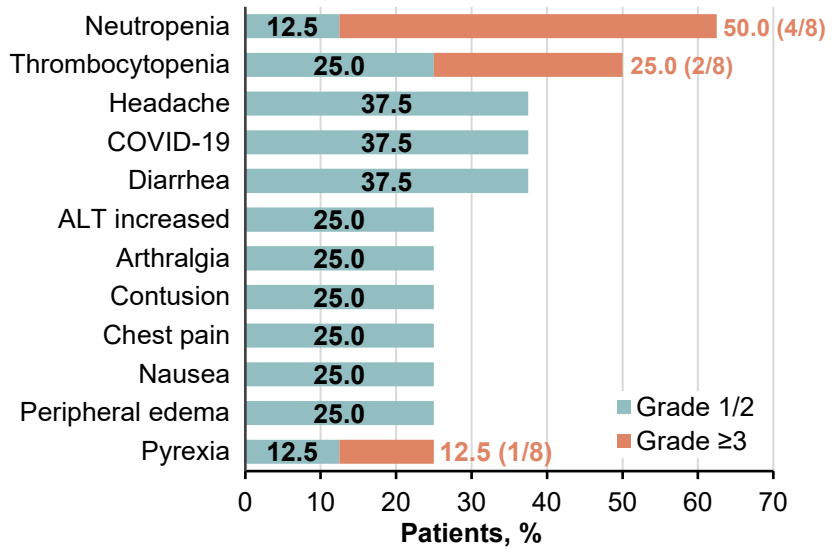
TEAE, n (%)	Sonrotoclax monotherapy (n=8)	Sonrotoclax + zanubrutinib (n=71)	All patients (N=79)
Any AEs	8 (100)	61 (86)	69 (87)
Grade ≥3	5 (63)	20 (28)	25 (32)
Serious AEs	2 (25)	7 (10)	9 (11)
Leading to death	0	0	0
Treated with sonrotoclax	**8**	**50**	**58**
Leading to hold of sonrotoclax	5 (62.5)	14 (28)	19 (33)
Leading to dose reduction of sonrotoclax	0	1 (2)	1 (2)
Leading to discontinuation of sonrotoclax	0	0	0

CLL, chronic lymphocytic leukemia; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; TEAE, treatment-emergent adverse event.

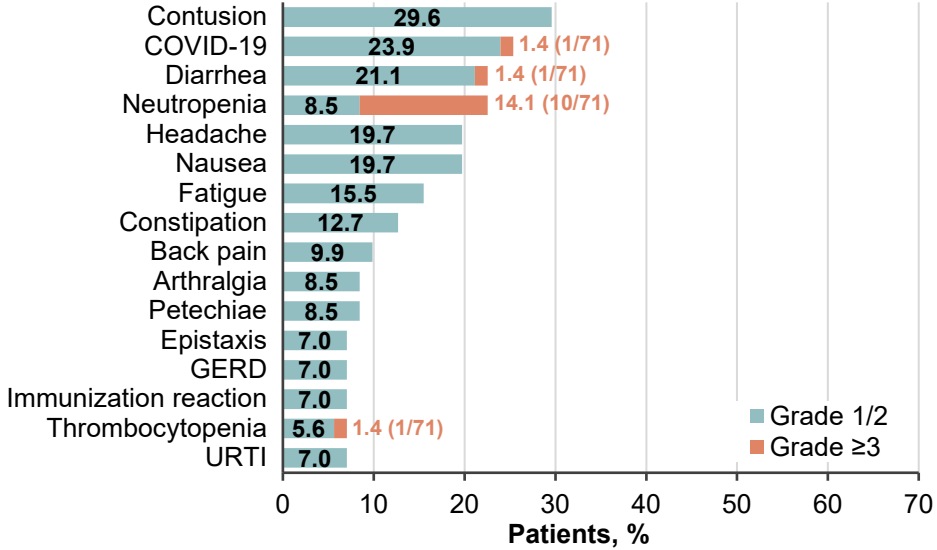
1. Soumerai et al. ASH 2022. Abstract 4201.

Most Frequent AEs

Sonrotoclax Monotherapy, n=8
(Events in ≥2 Patients)



Sonrotoclax + Zanubrutinib, n=71[a,b]
(Events in ≥5 Patients)



[a] Includes 21 patients who are still in zanubrutinib pretreatment phase and have not yet received sonrotoclax. [b] Includes 46 patients who are TN.
ALT, alanine transaminase; GERD, gastroesophageal reflux disease; TN, treatment-naive; URTI, upper respiratory tract infection.

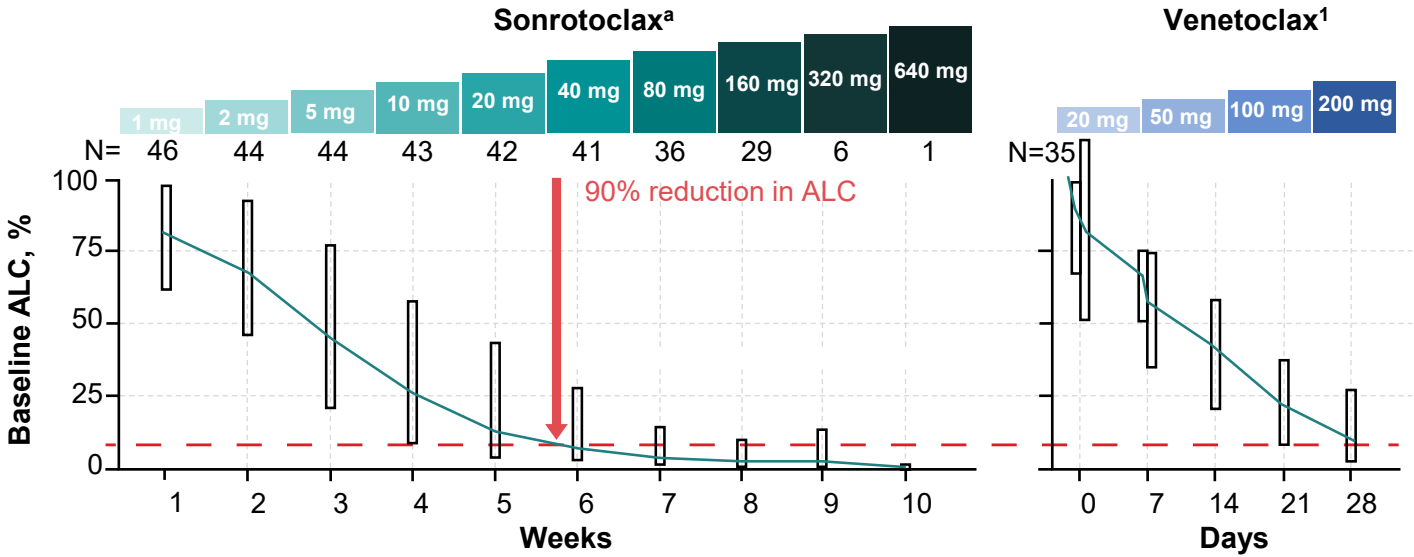
Selected TEAEs

- **TLS:** No clinical TLS and only 1 lab TLS observed
  - Patient with lab TLS had high tumor burden[a] receiving monotherapy with weekly ramp-up
    - The pre-dose urate was elevated; the phosphate level rose post-dose
  - No TLS was observed with daily ramp-up (TN combination at 320 mg; n=3)
- **GI toxicity:** Diarrhea was mostly grade 1
  - Monotherapy grade ≥2: 12.5%; combination grade ≥2: 5.6%; and grade 3: n=1
- **Neutropenia:**
  - G-CSF use[b]: monotherapy 4/8 (50%) patients; combination 10/71 (14.1%) patients
  - Only 3/78 (3.8%) patients used more than 1 course of G-CSF to treat neutropenia

[a] High tumor burden is any node ≥10 cm or a node 5-10 cm with an ALC ≥25x10^9/L. If a patient is not classified as "high" they are classified as "low."
[b] Includes all patients reporting G-CSF use during treatment, regardless of whether used for neutropenia or otherwise.
ALC, absolute lymphocyte count; G-CSF, granulocyte colony stimulating factor; GI, gastrointestinal; TLS, tumor lysis syndrome; TN, treatment-naive.

Reduction in ALC

- ALC dropped by ~90% after weekly ramp-up to 40 mg (sonrotoclax 40 mg ≈ venetoclax 200 mg [1:5])



Only data from patients with an ALC >5x10^9/L at baseline are included. Box plots represent median and 10th-90th percentiles. [a] Minimum ALC among 1 week of each dose level was used for calculation. N represents the number of patients who completed weekly dosing at dose level underneath. ALC data were pooled from both monotherapy (n=7) and combination therapy (n=39) cohorts because no difference was observed. ALC, absolute lymphocyte count.

1. Roberts et al. *N Engl J Med.* 2016;374(4):311-322.

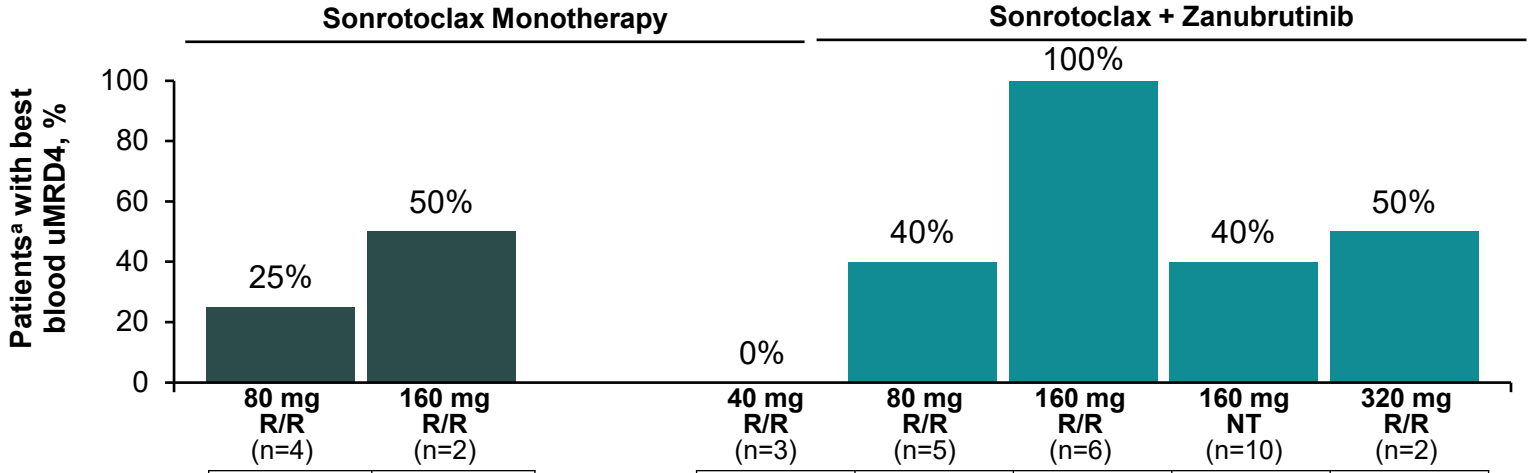
Overall Response Rate

	R/R sonrotoclax (n=8)	R/R sonrotoclax + zanubrutinib (n=25)	TN sonrotoclax + zanubrutinib (n=46)
Treated with sonrotoclax, n	**8**	**24**	**26**
Efficacy evaluable, n	**6**	**20[a]**	**11[a]**
ORR, n (%)	4 (67)	19 (95)	11 (100)
CR	2 (33)[b]	6 (30)[c]	2 (18)[d]
PR	2 (33)[e]	13 (65)[f]	9 (82)[g]
SD	2 (33)	1 (5)	0
PD	0	0	0
Median follow-up, months (range)	13.4 (1.4-21.9)	11.1 (2.2-18.6)	3.5 (0.4-9.7)

[a] n=2 (R/R) and n=11 (TN) have responded after zanubrutinib pretreatment but have not yet had response assessment on combination treatment and, therefore, are not included here. [b] 40 mg: n=1; 80 mg: n=1.
[c] 40 mg: n=1; 80 mg: n=2; 160 mg: n=3. [d] 160 mg: n=2. [e] 40 mg: n=1; 80 mg: n=1. [f] 40 mg: n=2; 80 mg: n=3; 160 mg: n=3 ; 320 mg: n=5. [g] 160 mg: n=9.
TN, treatment-naive.

Blood MRD

- Undetectable MRD (uMRD) in peripheral blood was observed at **≥80 mg** after **6 months** (monotherapy and combination in R/R CLL/SLL)
- **uMRD rate increased with longer follow-up and higher dose** (160 mg and 320 mg are immature)



	80 mg R/R (n=4)	160 mg R/R (n=2)	40 mg R/R (n=3)	80 mg R/R (n=5)	160 mg R/R (n=6)	160 mg NT (n=10)	320 mg R/R (n=2)
Median treatment duration, months (range)	**20.2** (15.9-23.8)	**14.3** (13.9-14.7)	**17.1** (16.4-17.8)	**15.0** (10.7-16.3)	**12.1** (9.8-13.7)	**8.2** (5.7-8.6)	**9.3** (9.0-9.5)
Median time to blood uMRD4[b], months (range)	**12.2** (12.2-12.2)	**7.4** (7.4-7.4)	**0**	**9.5** (6.7-12.2)	**8.1** (4.6-10.4)	**6.6** (4.9-6.9)	**7.1** (7.1-7.1)

Data cutoff date: 29 October 2022. MRD was measured by ERIC flow cytometry with 10^{-4} sensitivity. [a] In MRD-evaluable population, which was defined as patients who tested at least 1 postbaseline MRD sample. [b] From sonrotoclax first dose to first blood uMRD4; uMRD4 is defined as CLL cells out of total nucleated cells less than 10^{-4}.
CLL, chronic lymphocytic leukemia; MRD, minimal residual disease; SLL, small lymphocytic lymphoma; TN, treatment-naive; uMRD, undetectable minimal residual disease.

Conclusions

- Sonrotoclax, alone or in combination with zanubrutinib, was well tolerated
  - Dose escalation continues to 640 mg with only 1 DLT; MTD was not achieved
  - Grade ≥3 neutropenia and grade ≥2 diarrhea were uncommon and manageable
  - Only 1 laboratory TLS was seen; TLS was mitigated by the prophylactic measures and ramp-up schedule
- Efficacy is seen in monotherapy and in combination with zanubrutinib in R/R and in TN CLL/SLL
- Based on ALC reduction, sonrotoclax may be about 5 times as potent as venetoclax by dose
- MRD data are preliminary but appear promising
- A venetoclax-treated CLL/SLL cohort is recruiting

Acknowledgments

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Correspondence: ghia.paolo@hsr.it