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 Non-Hodgkin Lymphoma or Waldenström Macroglobulinemia: Preliminary Data

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HSANZ Haematology Society of Australia and New Zealand

ANZSBT Australian & New Zealand Society of Blood Transfusion Ltd

THANZ Thrombosis & Haemostasis society of Australia and New Zealand

Disclosures for Dr. Verner

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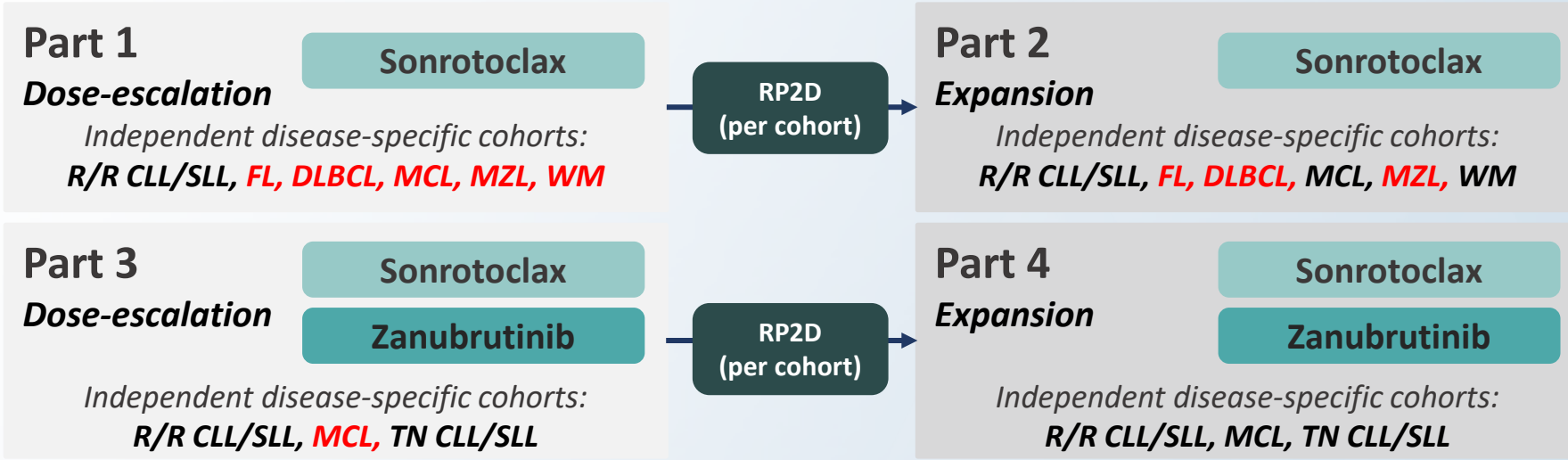
Introduction

- BCL2 inhibitors have been shown to be safe and effective for treating B-cell malignancies[1,2]
- Sonrotoclax (BGB-11417) is a more potent and selective BCL2 inhibitor than venetoclax in vitro and in xenograft mouse models of DLBCL[2,3]
- The combination of venetoclax and the BTK inhibitor, ibrutinib, in patients with R/R MCL or TN CLL/SLL appears to be effective, but the side effect profile can be problematic, with high rates of dose reductions and discontinuation[4,5]
- Zanubrutinib, a next-generation BTK inhibitor, achieved superior PFS with less atrial fibrillation and a favorable safety profile in head-to-head studies with ibrutinib in R/R CLL[6]
- Here, we present the preliminary results from a phase 1 trial (NCT04277637) of sonrotoclax monotherapy or in combination with zanubrutinib in patients with NHL

BCL2, B-cell lymphoma 2; CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; R/R, relapsed or refractory; SLL, small lymphocytic lymphoma; TN, treatment-naïve. 1. Kapoor et al. *Cell Death Dis.* 2020;11(11):941; 2. Hu et al. AACR 2020. Abstract 3077; 3. Hu et al. AACR 2020. Abstract 3077; 4. Wang et al. *J Hematol Oncol.* 2021;14(1):179; 5. Kater et al. *NEJM Evid.* 2022;1(7); 6. Hillmen et al. *Future Oncol.* 2020;16(10):517-523.

Study Design

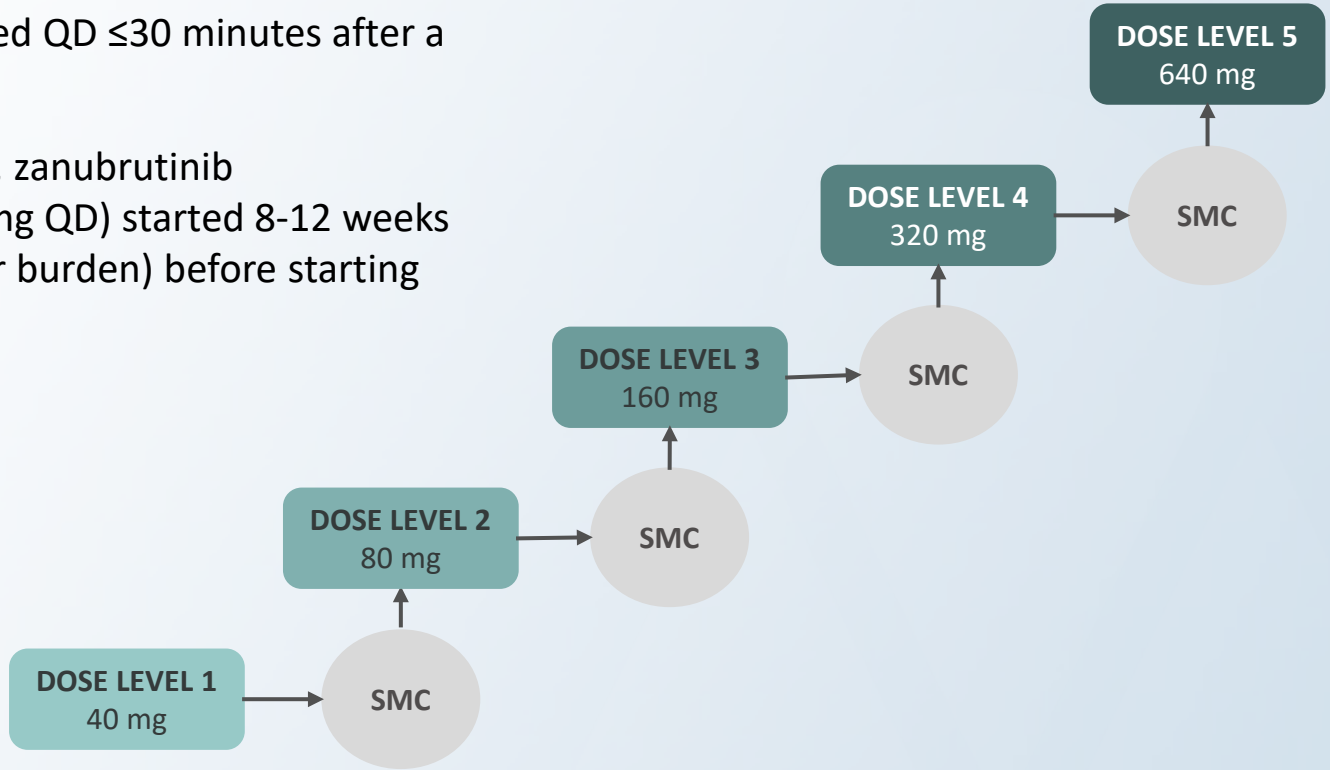
- BGB-11417-101 is a first-in-human, phase 1, open-label, multicenter, dose escalation and expansion study in patients with B-cell malignancies (NCT04277637)
- **Red:** NHL cohort data is the focus of this presentation



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
- In combination arms, zanubrutinib (160 mg BID or 320 mg QD) started 8-12 weeks (depending on tumor burden) before starting sonrotoclax

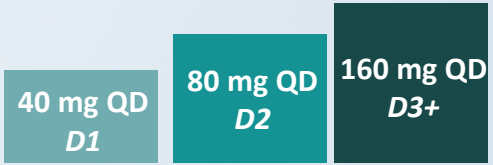


[a] Starting target dose level for a cohort may be >40 mg if established as safe in other cohorts after SMC review of dose-level cohort data.
SMC, safety monitoring committee.

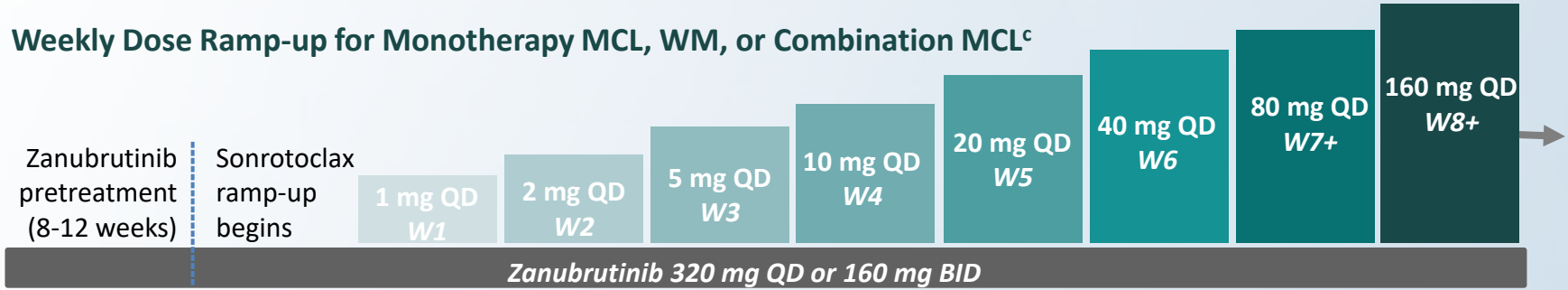
Dose Ramp-Up Schedules[a]

- All patients ramped-up sonrotoclax to the target dose
- TLS prophylaxis included:
  - Hydration started before each new dose level
  - Antihyperuricemics (allopurinol or rasburicase) started before first dose
- Hospitalization was initially required for the first 3 ramp-up doses, but requirement was later removed by SMC

3-Day Dose Ramp-Up for NHL[b]



Weekly Dose Ramp-up for Monotherapy MCL, WM, or Combination MCL[c]



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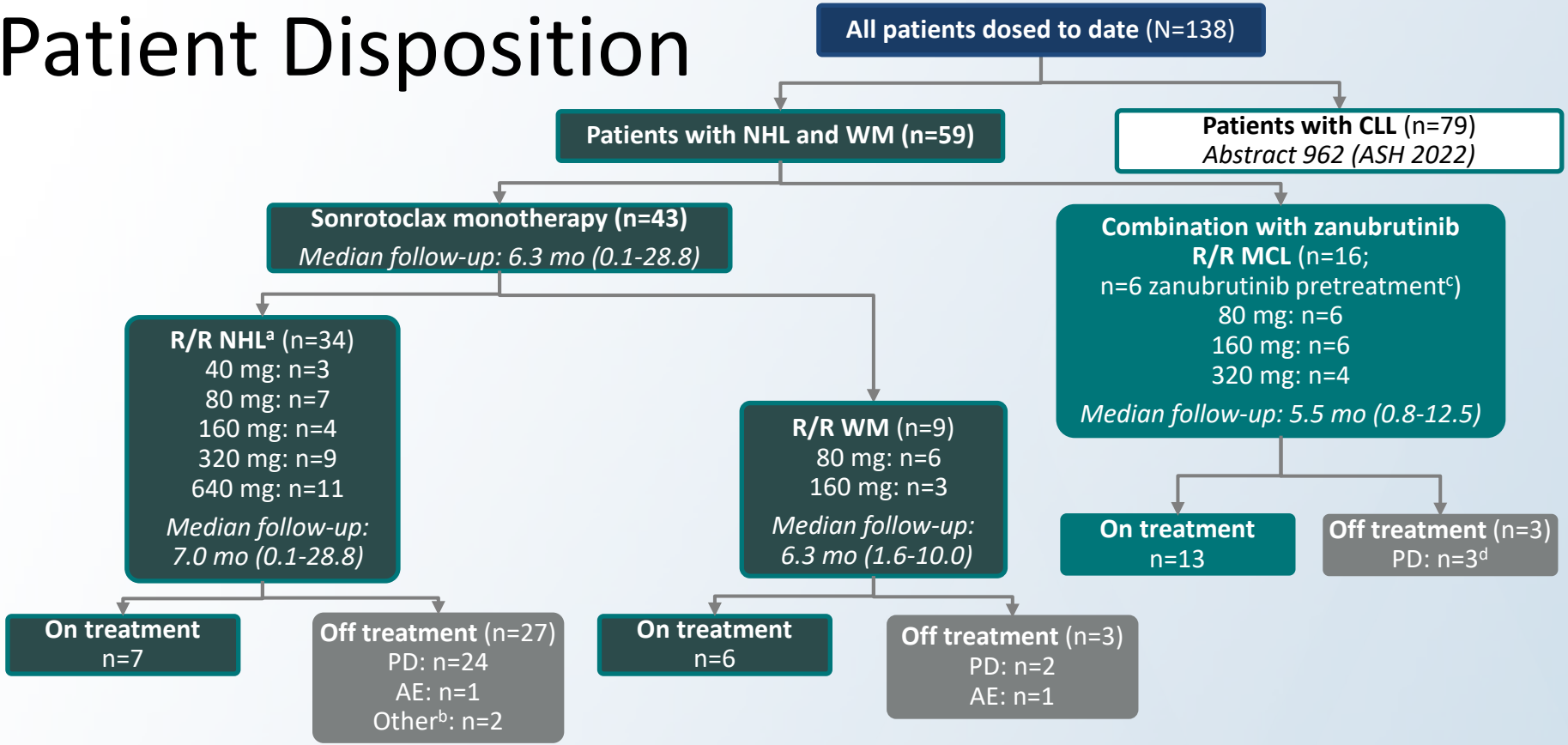
[a] Ramp-up will depend on target dose: examples show 160 mg target dose. [b] 3-day ramp-up doses vary depending on target dose: D1 25%, D2 50%, D3+ 100%. [c] Weekly ramp-up target doses follow the same weekly ramp-up schedule, stopping once they reach the target dose (lower target dose = shorter ramp-up). Ramp-up is identical for monotherapy.

MCL, mantle cell lymphoma; SMC, safety monitoring committee; TLS, tumor lysis syndrome; W, week; WM, Waldenström macroglobulinemia.

Patient Disposition



Data cutoff date: 01 Sep 2022. [a] Includes DLBCL (n=18), FL (n=6), MZL (n=7), MCL (n=3). [b] Includes other or physician decision.
[c]Patients who are still in the zanubrutinib pretreatment phase and have not yet received sonrotoclax.
[d] One patient progressed on zanubrutinib pretreatment before receiving sonrotoclax.
CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; mo, months; TN, treatment-naive; WM, Waldenström macroglobulinemia.

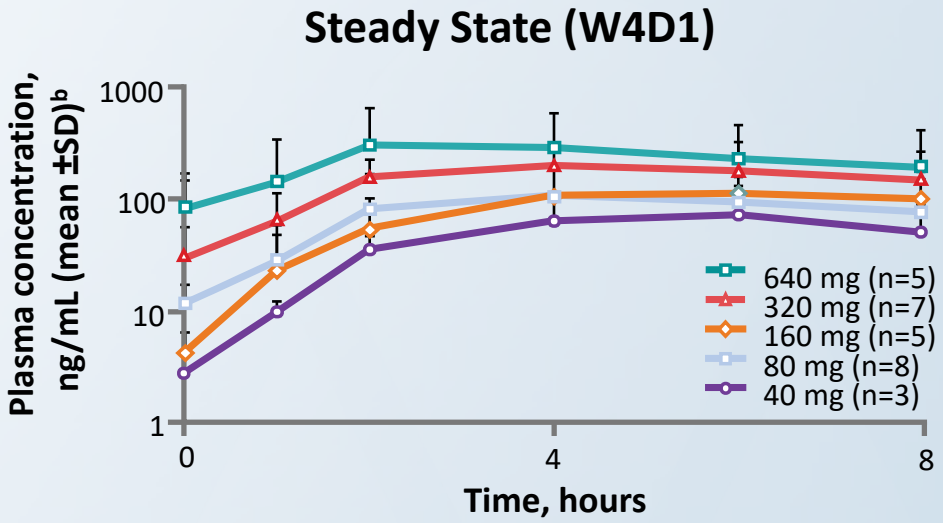
Patient Characteristics

Characteristic	Sonrotoclax monotherapy (n=43)	Sonrotoclax + zanubrutinib (n=16)	All patients (N=59)
Median age, (range), years	71 (48-86)	62 (45-85)	70 (45-86)
Sex, n (%)			
Male	30 (70)	12 (75)	42 (71)
Female	13 (30)	4 (24)	17 (29)
ECOG PS, n (%)			
0	18 (42)	7 (44)	25 (42)
1	22 (51)	8 (50)	30 (51)
2	3 (7)	0	3 (5)
Unknown	0	1 (6)	1 (2)
Disease type, n (%)			
DLBCL	18 (42)	0	18 (31)
FL	6 (14)	0	6 (10)
MZL	7 (16)	0	7 (12)
MCL	5 (12)	16 (100)	21 (36)
WM	9 (21)	0	9 (15)
No. of prior lines of therapy, median (range)	2 (1-8)	1 (1-3)	2 (1-8)
Time from last therapy, median (range), months	3.1 (0-158)	15.9 (3-64)	8.5 (0-158)

All enrolled patients were R/R. ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinemia.

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}, time to max concentration; W, week.

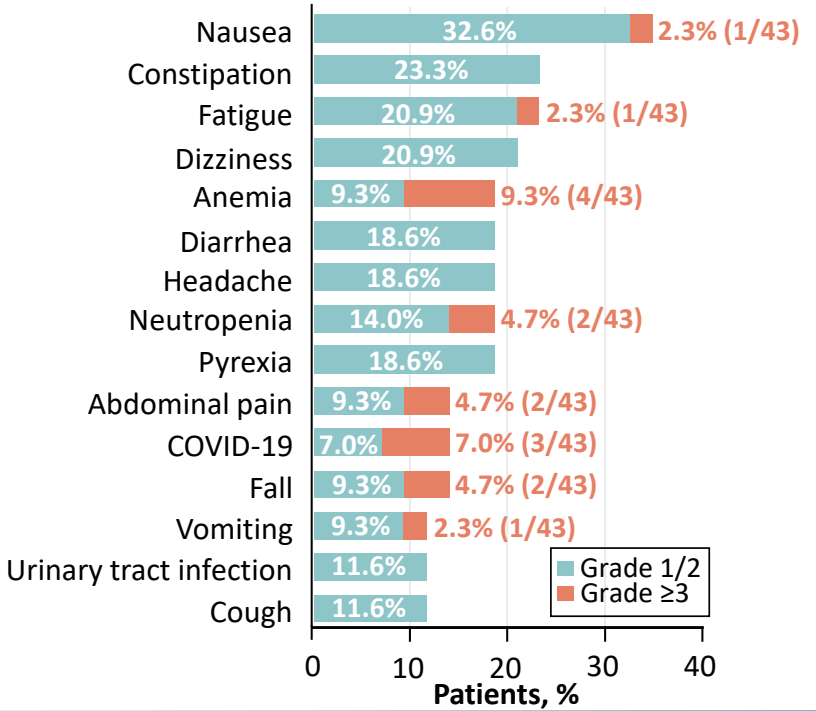
Summary of AEs

Patients, n (%)	Sonrotoclax monotherapy (n=43)	Sonrotoclax + zanubrutinib (n=16[a])
Any AEs	40 (93)	13 (81)
Grade ≥3	20 (47)	6 (38)
Serious AEs	17 (40)	5 (31)
Leading to death	3 (7)[b]	2 (13)[c]
Treated with sonrotoclax	43	10
Leading to hold of sonrotoclax[d]	9 (21)	4 (40)[e]
Leading to dose reduction of sonrotoclax	1 (2)[f]	0
Leading to discontinuation of sonrotoclax	2 (5)[g]	0

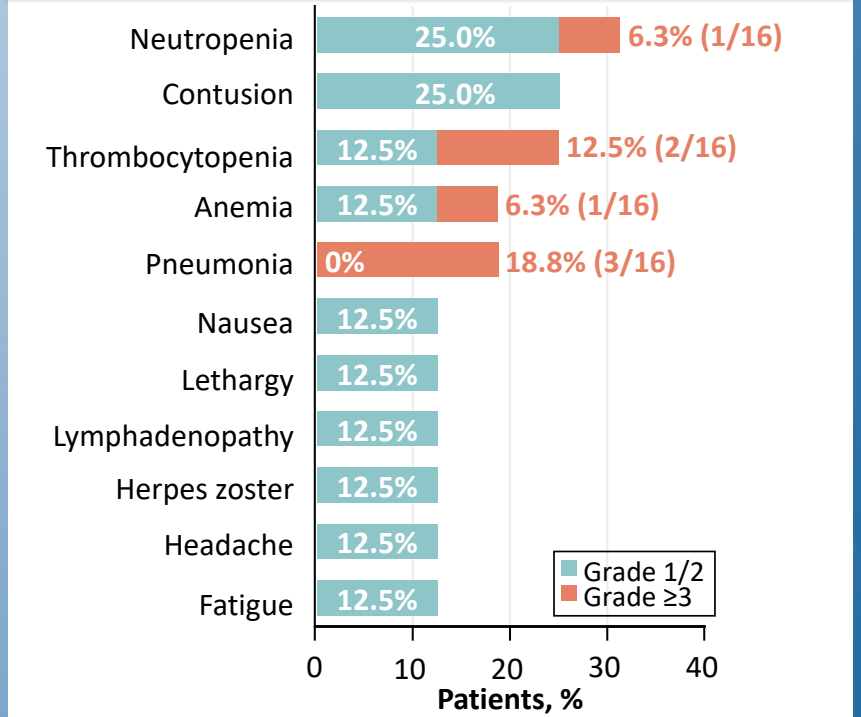
[a] All patients on combination therapy have MCL; Includes 6 patients who have only received zanubrutinib. [b] GI hemorrhage, COVID-19 pneumonia death secondary to progression. [c] Cardiac arrest (not drug related), pleural effusion. [d] Pneumonia, sepsis, vomiting, CMV reactivation, worsening nausea, febrile neutropenia, COVID-19 pneumonia, ALT increased, AST increased, GGT increased, small intestinal obstruction, GI hemorrhage, platelet count decreased, diverticulitis, COVID-19, neutropenia. [e] Diarrhea, pneumonia, pleural effusion, lymph node pain, lymphadenopathy. [f] Gingival pain, fatigue, weight loss. [g] COVID-19 pneumonia; GI hemorrhage.
ALT, alanine transaminase; AST, aspartate aminotransferase; CMV, cytomegalovirus; GGT, gamma-glutamyl transferase; GI, gastrointestinal; MCL, mantle cell lymphoma.

Most Frequent AEs (in ≥ 10% of Patients)

Sonrotoclax monotherapy



Sonrotoclax + zanubrutinib[a]



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[a] Includes n=6 patients who are still in the zanubrutinib pretreatment phase and have not yet received sonrotoclax; All patients who received combination therapy have MCL.
MCL, mantle cell lymphoma.

Selected Adverse Events

- **TLS:** One case of laboratory TLS was observed
  - In MZL patient after first dose of 160 mg, given 7 days before day 1 (as part of a food effect evaluation)
  - Lab changes resolved within 24 hours with supportive care; received full planned dosing from day 1 with no recurrence of TLS
- **GI toxicity:**
  - All cases were mild; grade ≥3 nausea or vomiting only seen in 1 patient each
  - Diarrhea was mostly grade 1, with grade 2 observed in 2 patients
- **Neutropenia:**
  - Cases were typically mild; grade ≥3 seen in 2 who received monotherapy and 1 who received combination therapy
  - Febrile neutropenia occurred in 2 patients (monotherapy)
  - Among 12 patients who received G-CSF (median course 3 days), 3 received >1 course during treatment

G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; MZL, marginal zone lymphoma; TLS, tumor lysis syndrome.

DLTs

- Only 1 DLT of febrile neutropenia was noted among patients with NHL
- DLT occurrence was not dose dependent, and zanubrutinib combination did not appear to increase the risk
- Findings are consistent with previous sonrotoclax CLL data with doses up to 320 mg not reaching the MTD so far

DLTs, n/N	40 mg	80 mg	160 mg	320 mg	640 mg
Sonrotoclax (NHL)	0/3	0/4	1/4	0/9	0/6
Sonrotoclax (WM)	-	0/5	TBD	TBD	TBD
Sonrotoclax + zanubrutinib (MCL)	-	0/5	0/3	TBD	TBD

CLL, chronic lymphocytic leukemia; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; MCL, mantle cell lymphoma; TBD, to be determined; WM, Waldenström macroglobulinemia.

Overall Response Rate

	Sonrotoclax monotherapy (n=43)		Sonrotoclax + zanubrutinib (n=46)
	R/R NHL, DLBCL, MZL, FL, tFL, MCL (n=34)[a]	R/R WM (n=9)[b]	R/R MCL (n=16)[c]
Treated with sonrotoclax, n	34	9	10
Efficacy evaluable, n	29[d]	7	9
Best overall response[e], n (%)	3 (10)	3 (43)	7 (78)
CR	1 (3)	0	6 (67)
PR	2 (7)	3 (43)	1 (14)
SD	7 (24)	2 (29)	0
PD	18 (62)	1 (14)	2 (22)
Discontinued before assessment, n (%)	1 (3)	1 (14)	0
Median follow-up, months (range)	7 (0.1-29)	6 (2-10)	5 (1-13)

[a] At 40 mg: n=3; 80 mg: n=7; 160 mg: n=4; 320 mg: n=9; 640 mg: n=11. [b] At 80 mg: n=6; 160 mg: n=3. [c] At 80 mg: n=12; 160 mg: n=4.
[d] One patient with MCL on monotherapy was efficacy evaluable. [e] PR or better.
MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; tFL, transformed follicular lymphoma; WM, Waldenström macroglobulinemia.

Conclusions

- Sonrotoclax monotherapy is tolerable in patients with NHL or WM at doses up to 640 mg and MTD was not reached
- Sonrotoclax (up to 320 mg) + zanubrutinib combination was well tolerated in patients with MCL, with dose escalation ongoing
- No clinical TLS was observed; 1 case of laboratory TLS on monotherapy resolved within 24 hours
- These data demonstrate the preliminary efficacy of sonrotoclax monotherapy (NHL, WM) and in combination with zanubrutinib (MCL), with more responses observed at higher dose levels
- The study continues to assess the RP2D in monotherapy and combination therapy

DLT, dose-limiting toxicity; MTD, maximum tolerated dose; MCL, mantle cell lymphoma; RP2D, recommended phase 2 dose; TLS, tumor lysis syndrome; WM, Waldenström macroglobulinemia.

Acknowledgments

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