First-Line Treatment of CLL/SLL With the All-Oral Combination of Sonrotoclax and Zanubrutinib Achieves Undetectable Minimal Residual Disease Rates Of >90%, Including in Patients With del(17p)/*TP53*

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CONCLUSIONS

- Sonrotoclax in combination with zanubrutinib was well tolerated with a favorable safety profile, and achieved uMRD rates of >90%, (uMRD5 of 87.3% for 320-mg cohort) including in patients with high-risk cytogenetics and unmutated IGHV genotype
- No cases of laboratory or clinical tumor lysis syndrome occurred
  - No fatal TEAEs or death occurred and the majority of TEAEs were low grade; low rates of transient gastrointestinal TEAEs, predominantly grade 1, were observed
  - The most common grade ≥3 TEAE was neutropenia, which was transient
- The depth and kinetics of uMRD achieved with sonrotoclax + zanubrutinib highlights the improved potency and differentiated profile of this combination versus available combination therapies in first-line CLL
- Sonrotoclax in combination with zanubrutinib is being evaluated in patients with TN CLL in two phase 3 clinical trials (NCT06073821, NCT07277231)

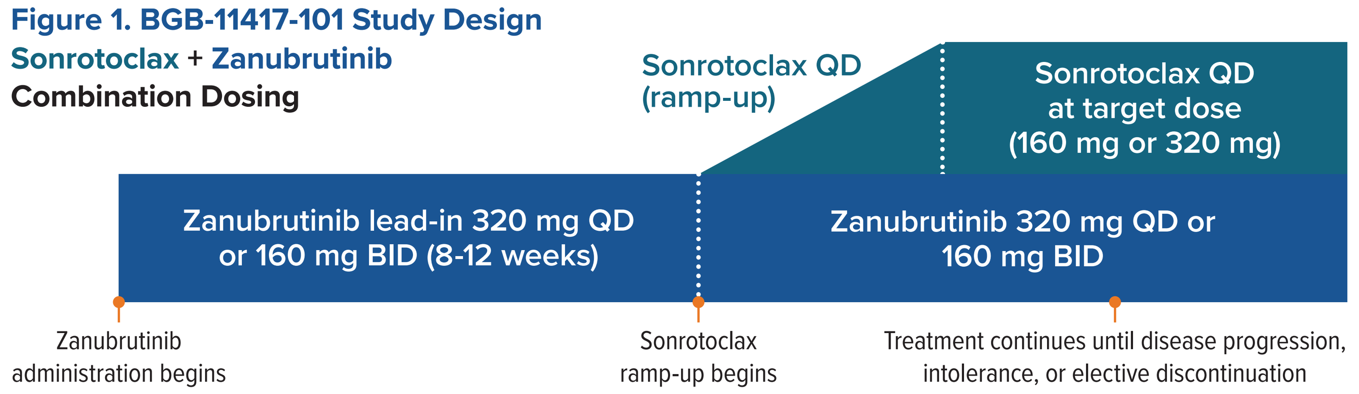
INTRODUCTION

- Oral, fixed-duration Bruton tyrosine kinase (BTK) inhibitor/B-cell lymphoma 2 (BCL2) inhibitor combinations are effective and convenient options for first-line treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)[1]
  - However, current combination regimens achieve suboptimal undetectable minimal residual disease (uMRD) rates, highlighting a need for more effective time-limited oral doublet therapies to improve depth of response
- Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is more selective and pharmacologically potent than venetoclax, with an optimized pharmacokinetic profile characterized by a shorter half-life and minimal drug accumulation[2,3]
- Zanubrutinib is a second-generation BTK inhibitor designed for greater kinase selectivity and sustained BTK occupancy, and is highly effective in patients with treatment-naive (TN) and relapsed/refractory CLL/SLL[4]
- Here, we report updated results from the BGB-11417-101 trial in patients with TN CLL/SLL treated with sonrotoclax in combination with zanubrutinib

METHODS

- BGB-11417-101 (NCT04277637) is a global phase 1/1b study evaluating sonrotoclax as monotherapy, or in combination with zanubrutinib and/or obinutuzumab in patients with B-cell malignancies (**Figure 1**); here, we report data from cohorts receiving combination zanubrutinib and sonrotoclax in TN CLL/SLL
- Treatment consisted of 8-12 weeks of zanubrutinib lead-in (320 mg QD or 160 mg BID), after which sonrotoclax was added with a ramp-up to the target dose (160 or 320 mg)
- Patients were treated until progression, unacceptable toxicity, or protocol-defined elective discontinuation after 96 weeks of combination treatment at target dose
- The primary objective was to determine the recommended phase 2 dose (RP2D) of sonrotoclax, and to evaluate safety and tolerability
- Secondary endpoints included overall response rate (ORR), defined as partial response with lymphocytosis (PR-L) or better
- Exploratory endpoints included uMRD4 rates in peripheral blood per flow cytometry and next generation-sequencing (NGS)

Figure 1. BGB-11417-101 Study Design



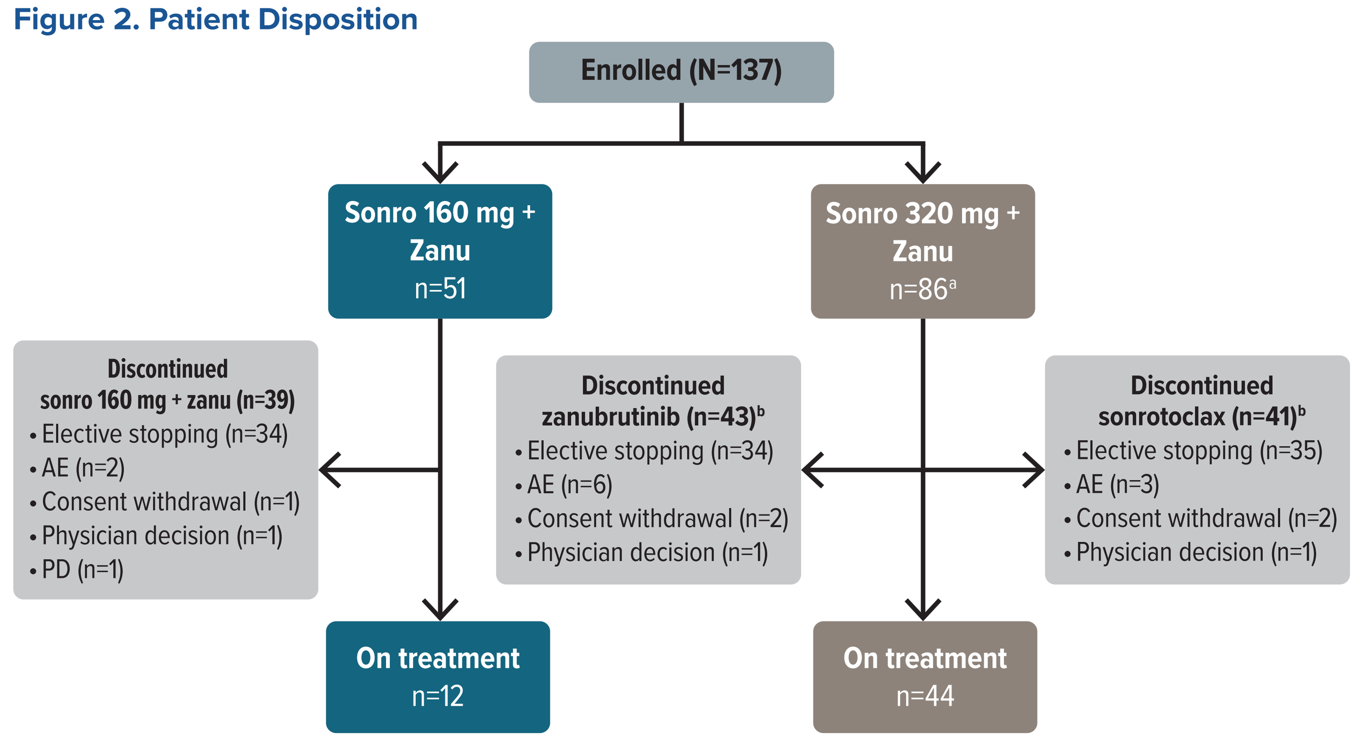
Abbreviations: BID, twice daily; QD, once daily.

RESULTS

Patient Population

- At time of reporting, 137 patients with TN CLL/SLL were enrolled in sonrotoclax 160-mg (n=51) and 320-mg (n=86) cohorts in combination with zanubrutinib (**Figure 2**)
  - After a median follow-up of 33.6 months (range, 3.1-48.8 months), 94.9% (130/137) remained on the study
  - Of patients who discontinued sonrotoclax, 86.3% (69/80) did so electively after 96 weeks at target dose
  - The rate of elective discontinuation of sonrotoclax in the 320-mg cohort was similar to the overall population (85.4%; 35/41)

Figure 2. Patient Disposition



[a]One patient received zanubrutinib but had not received sonrotoclax treatment. [b]In the 320-mg cohort, 43 participants discontinued any study drug (sonrotoclax and/or zanubrutinib). Per-drug numbers differ due to one patient who did not receive sonrotoclax and one who discontinued only zanubrutinib.

Abbreviations: AE, adverse event; PD, progressive disease; sonro, sonrotoclax; zanu, zanubrutinib.

- Median age was 62 years (range, 32-84) and 71.5% of patients were male (**Table 1**)
- At baseline, 28.5% (39/137) had high tumor burden, 59.9% (82/137) had confirmed unmutated IGHV, and 13.1% (18/137) had confirmed del(17p) and/or *TP53* mutations

Table 1. Demographic and Clinical Characteristics of Patients at Baseline

Characteristics	Sonro 160 mg + Zanu (n=51)	Sonro 320 mg + Zanu (n=86)	All Patients (N=137)
Follow-up time, median (range), mo	33.2 (17.5-48.8)	34.1 (3.1-45.2)	33.6 (3.1-48.8)
Age, median (range), years	63.0 (38-82)	61.0 (32-84)	62.0 (32-84)
≥65 years, n (%)	20 (39.2)	35 (40.7)	55 (40.1)
Male, n (%)	37 (72.5)	61 (70.9)	98 (71.5)
Disease type, n (%)			
CLL	48 (94.1)	82 (95.3)	130 (94.9)
SLL	3 (5.9)	4 (4.7)	7 (5.1)
Risk status, n (%)			
del(17p) or *TP53* mutation, n (%)	7 (13.7)	11 (12.8)	18 (13.1)
del(11q)	10 (19.6)	11 (12.8)	21 (15.3)
Unmutated IGHV, n (%)	34 (66.7)	48 (55.8)	82 (59.9)
High tumor burden at baseline, n (%)[a]	22 (43.1)	17 (19.8)	39 (28.5)

[a]Any lymph node ≥10 cm or lymph node ≥5 cm and absolute lymphocytes count ≥25×10⁹/L

Abbreviations: CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain variable; mo, months; SLL, small lymphocytic lymphoma; sonro, sonrotoclax; zanu, zanubrutinib.

Safety

- Most treatment-emergent adverse events (TEAEs) occurred at grades 1 and 2, and no TEAE led to death (**Table 2**)
  - Five patients (3.6%) discontinued sonrotoclax due to TEAEs
  - No clinical or laboratory tumor lysis syndrome occurred

Table 2. Treatment-Emergent Adverse Events and Safety Data (As-Treated Population)

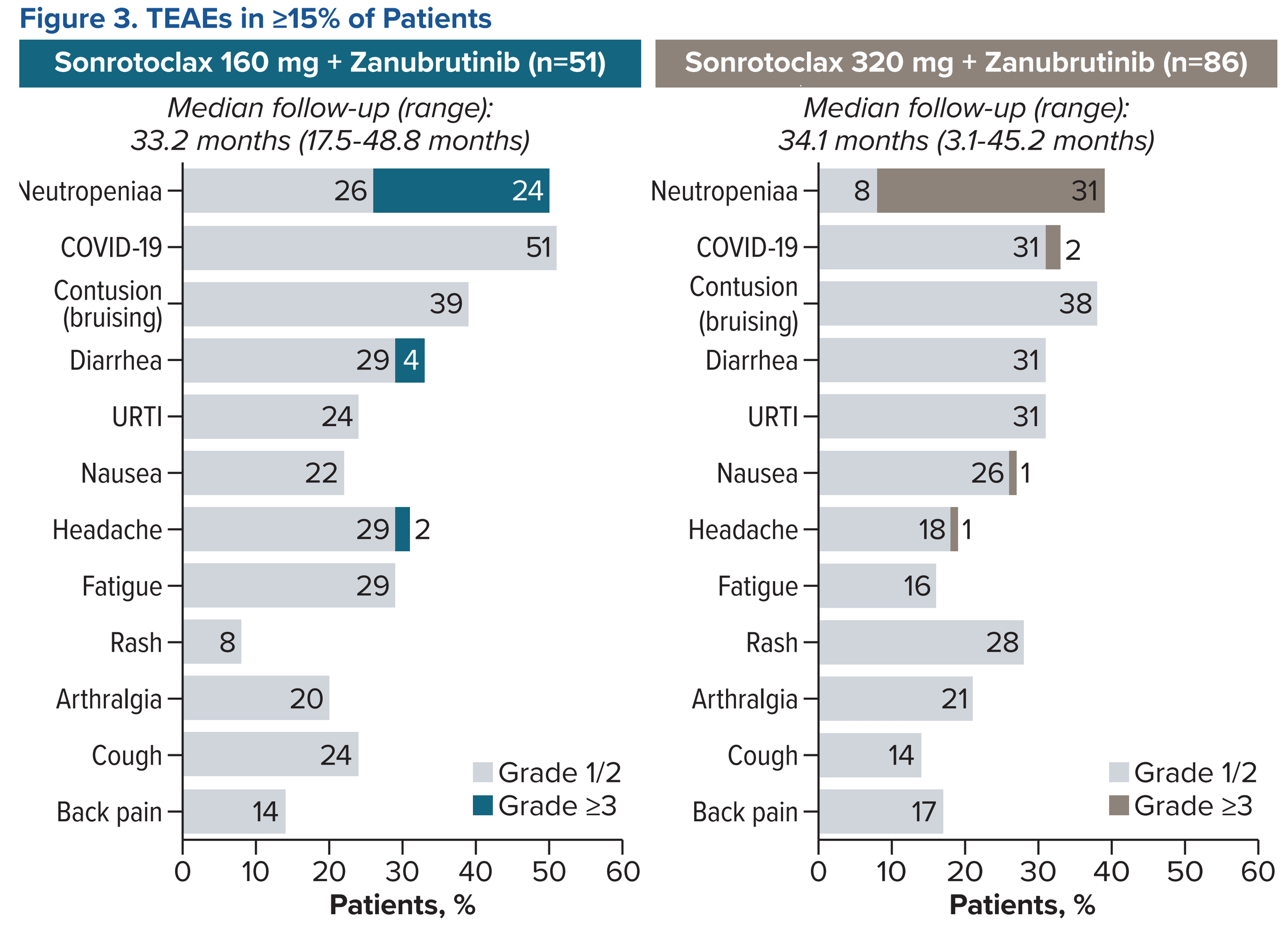
Patients, n (%)	Sonro 160 mg + Zanu (n=51)	Sonro 320 mg + Zanu (n=86)[a]	All Patients (N=137)
Any TEAEs	51 (100.0)	85 (98.8)	136 (99.3)
Grade ≥3	35 (68.6)	52 (60.5)	87 (63.5)
Serious TEAEs	20 (39.2)	27 (31.4)	47 (34.3)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Leading to discontinuation of zanu	2 (3.9)	6 (7.0)	8 (5.8)
Treated with sonro			
Leading to discontinuation of sonro	2 (3.9)	3 (3.5)	5 (3.6)
Relative dose intensity of sonro, median, %	98.9	99.0	99.0
Duration of exposure, median (range), mo	29.1 (5.8-48.8)	26.2 (0.8-45.2)	26.7 (0.8-48.8)

[a]One patient received zanubrutinib but had not received sonrotoclax treatment.

Abbreviations: mo, months; sonro, sonrotoclax; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.

- The most common any-grade TEAEs were neutropenia (43.1%), COVID-19 (40.1%), contusion/bruising (38.7%), and diarrhea (32.1%) (**Figure 3**)
  - The most common grade ≥3 TEAE was neutropenia (28.5%)
  - Rates of diarrhea were similar across dose cohorts, with no grade ≥3 events in the 320-mg cohort

Figure 3. TEAEs in ≥15% of Patients



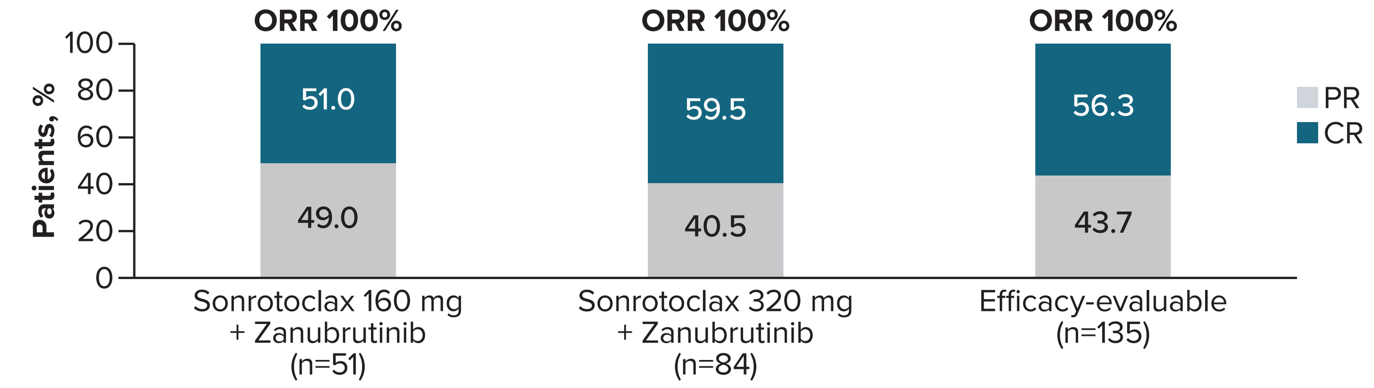
[a]Includes the combined preferred terms *neutrophil count decreased* and *neutropenia*.

Abbreviations: mo, month; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Efficacy

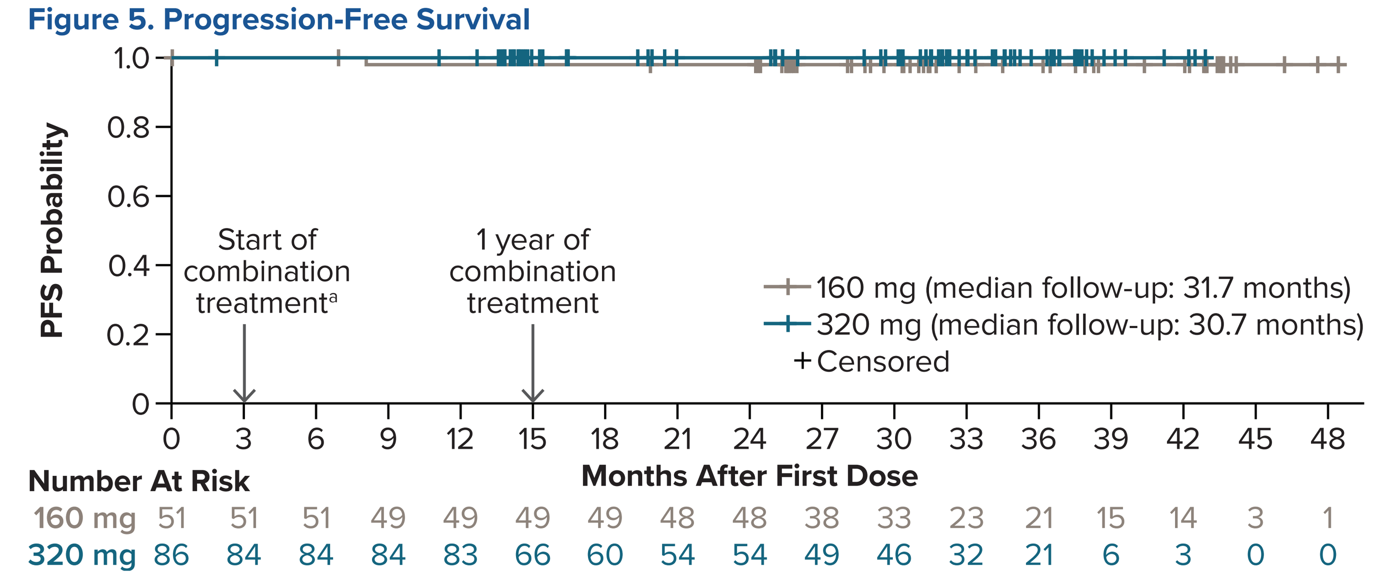
- In 135 efficacy-evaluable patients, ORR was 100%, with complete response (CR) rates of 51.0%and 59.5% in the 160- and 320-mg cohorts, respectively (**Figure 4**)
- Median time to first response was 2.6 months (range, 1.5-10.8 months)
- At a median follow-up of 30.7 months, no progression was observed in the 320-mg cohort, including the 35 patients who electively discontinued zanubrutinib or sonrotoclax (median treatment-free duration, 9.8 months [range, 2.7-15.5 months]) (**Figure 5**)
  - Across both dose levels, 70 patients electively discontinued zanubrutinib or sonrotoclax after 96 weeks at target dose with a median treatment-free duration of 9.2 months (range, 0.6-21.6 months)
- In the 320 mg group, best blood uMRD4 rates by weeks 24, 48, and 96 were 81.2% (69/85), 91.8% (78/85), and 98.2% (55/56), respectively (**Figure 6A**)
- Across all cohorts, rates of uMRD4 by 96 weeks were consistent regardless of IGHV or del(17p)/*TP53* mutation status (**Figure 6B**)
- In the 320 mg group, best blood uMRD5 rate as measured by next-generation sequencing was 87.3% (69/79) (**Figure 6C**)
- Across cohorts, median time from sonrotoclax target dose to first blood uMRD4 was 4.6 months (range, 1.3-32.9 months)
- Time to uMRD4 in the 320 mg cohort was similar, regardless of IGHV mutation status (mutated: median 4.5 months; unmutated: median 5.2 months) (**Figure 7**)

Figure 4. Overall Response Rates



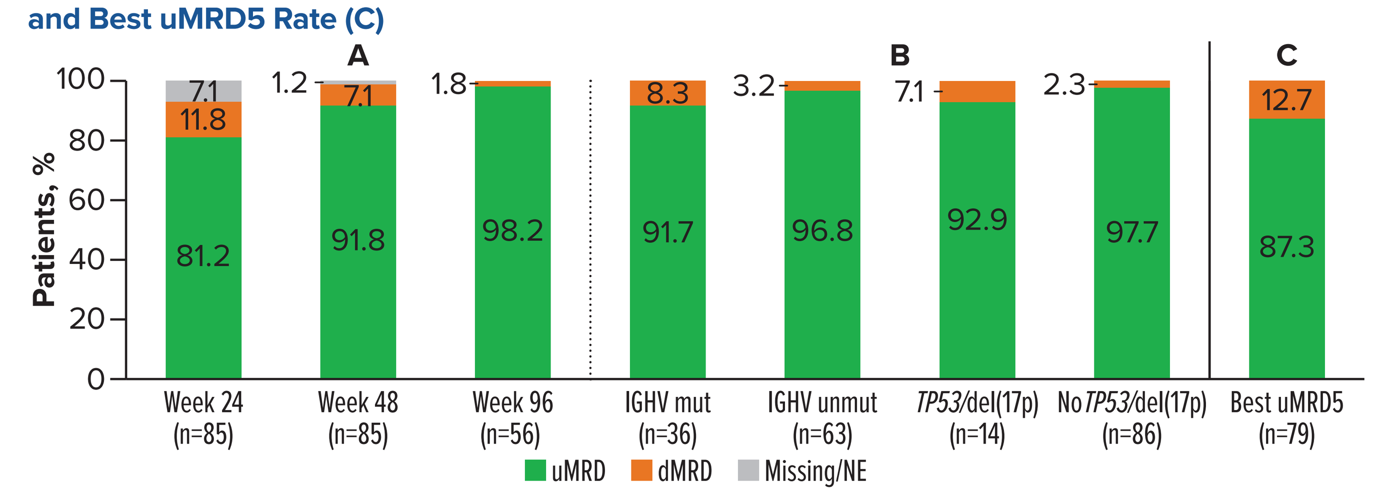
Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response.

Figure 5. Progression-Free Survival



[a]Zanubrutinib lead-in was 8-12 weeks.

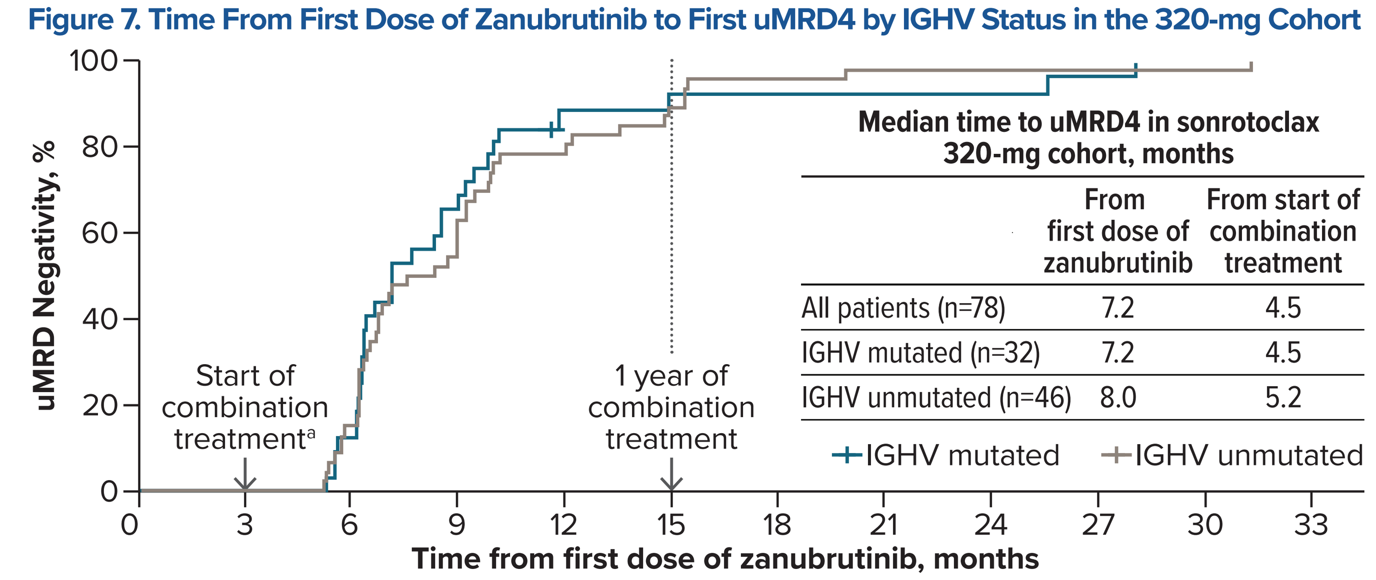
Figure 6. Best uMRD4 Rates Over Time (320 mg) (A), by Week 96 by Subgroup (All Cohorts) (B), and Best uMRD5 Rate (C)



Percentages are based on number of patients who should have reached each week on target dose.

Abbreviations: CLL, chronic lymphocytic leukemia; dMRD, detectable minimal residual disease; IGHV, immunoglobulin heavy chain variable; NE, not evaluable; uMRD4, undetectable minimal residual disease at <1 CLL cell per 10,000 leukocytes ($<10^4$) , uMRD5, undetectable minimal residual disease at <1 CLL cell per 100,000 leukocytes ($<10^5$).

Figure 7. Time From First Dose of Zanubrutinib to First uMRD4 by IGHV Status in the 320-mg Cohort



Median time to uMRD4 in sonrotoclax 320-mg cohort, months

	From first dose of zanubrutinib	From start of combination treatment
All patients (n=78)	7.2	4.5
IGHV mutated (n=32)	7.2	4.5
IGHV unmutated (n=46)	8.0	5.2

[a]Zanubrutinib lead-in was 8-12 weeks.

Abbreviations: CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain variable; NE, not evaluable; uMRD4, undetectable minimal residual disease at <1 CLL cell per 10,000 leukocytes ($<10^4$).

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