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Combination Treatment With Sonrotoclax + Zanubrutinib is Well Tolerated and Achieves Deep Responses in Patients With Treatment-Naive CLL/SLL: Data From an Ongoing Phase 1/2 Study

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Disclosures of Paolo Ghia

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

Introduction

- Sonrotoclax is a BH3 mimetic that binds and inhibits BCL2
 - >10-fold potency compared with venetoclax¹ 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 models²⁻⁵
- Ibrutinib with venetoclax in patients with CLL/SLL is effective; however, toxicities can limit use⁶
- 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 favorable safety profile, including less cardiovascular toxicity than ibrutinib in R/R CLL/SLL^{8,9}
- 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

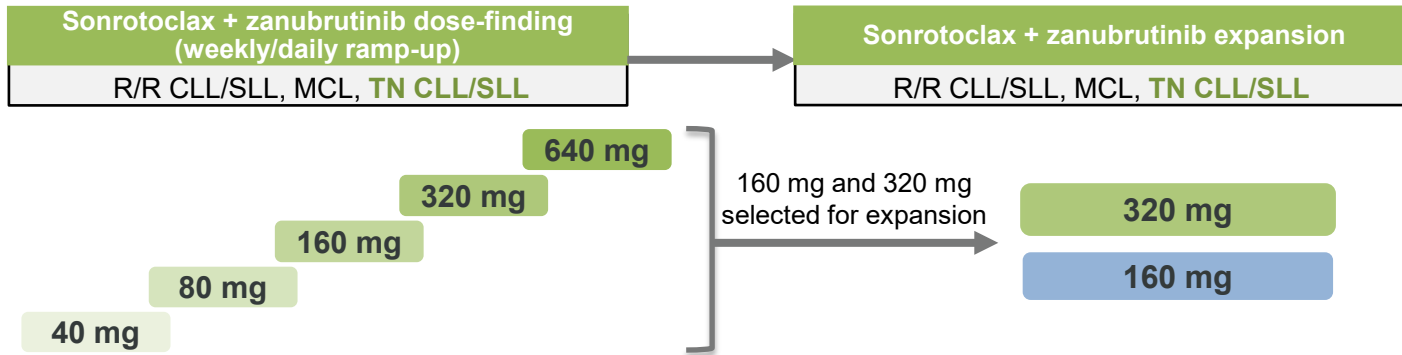
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Study Design and Methods

- 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)



- 8-12 wks of zanubrutinib monotherapy was given prior to sonrotoclax dosing (12 wks 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	Sonro 160 mg + zanu (n=51)	Sonro 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 <i>TP53</i> ^{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 >25×10⁹/L.

Dose Modification and AE Summary

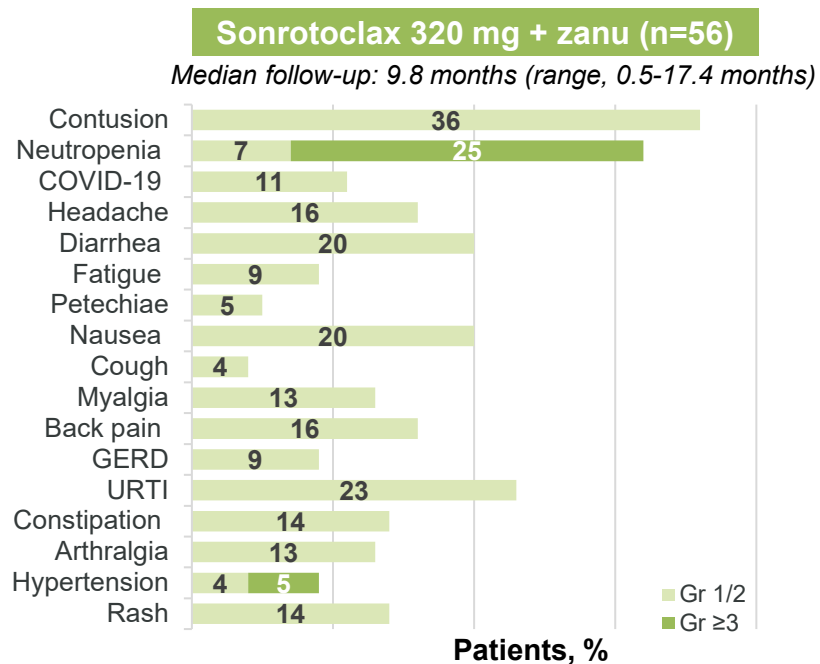
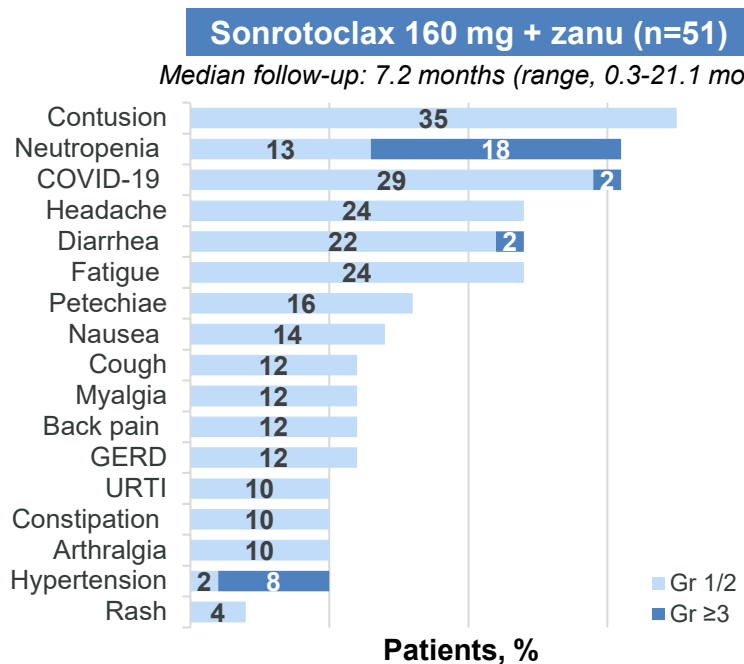
- Sonrotoclax in combination with zanubrutinib is well tolerated and generally favorable, with very low rates of treatment discontinuation and dose reductions

	Sonro 160 mg + zanu (n=51)	Sonro 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)

^aOne 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

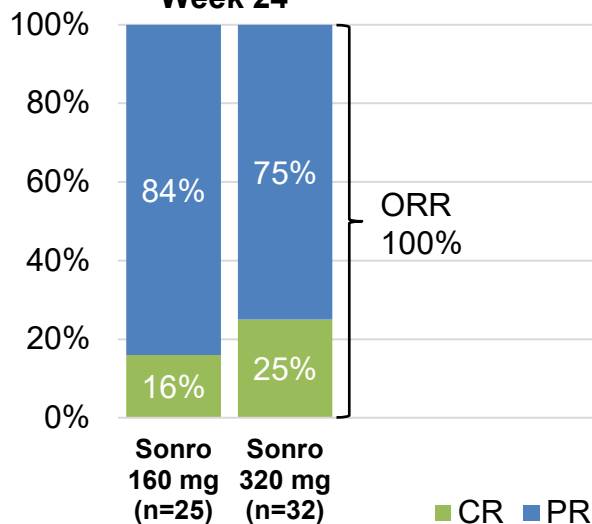
TLS^a	No clinical or laboratory TLS was observed with weekly or daily ramp-up
GI toxicity^b	Diarrhea events were mostly grade 1; no dose reductions occurred
Atrial fibrillation	No atrial fibrillation was observed
Neutropenia	Most frequent AE (and grade ≥ 3 AE); 1 dose reduction/no dose holds, 18 patients (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.

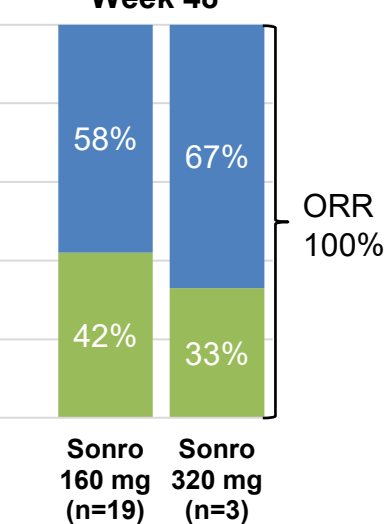
Overall Response Rate

Response rates improved with time

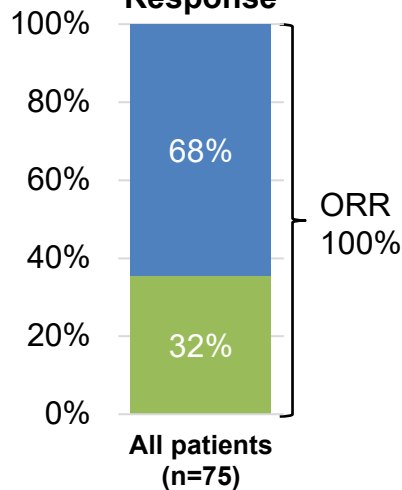
Best Response^a by Week 24



Best Response^a by Week 48



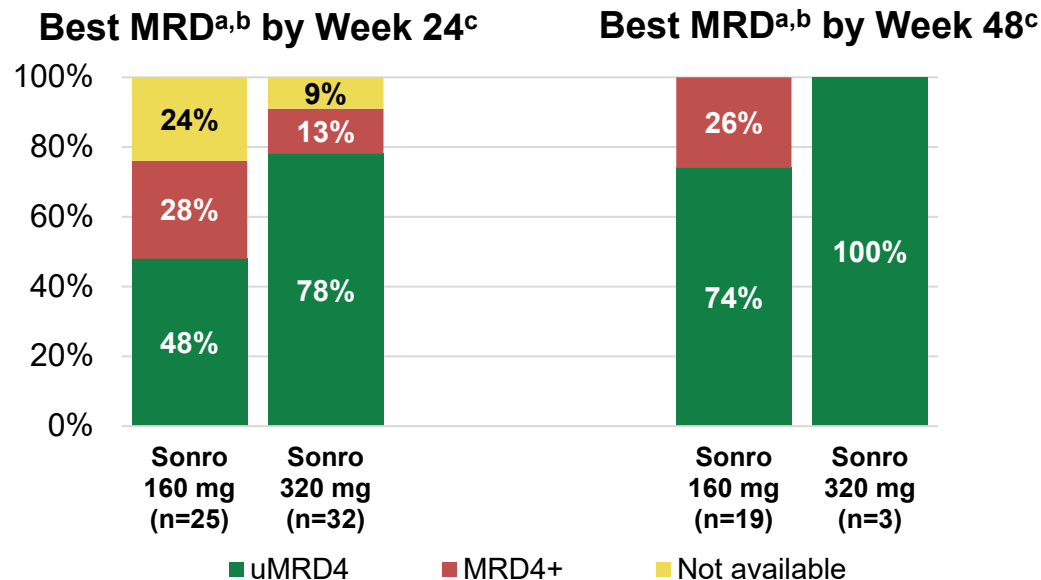
Best Overall Response



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

Minimal Residual Disease in Peripheral Blood

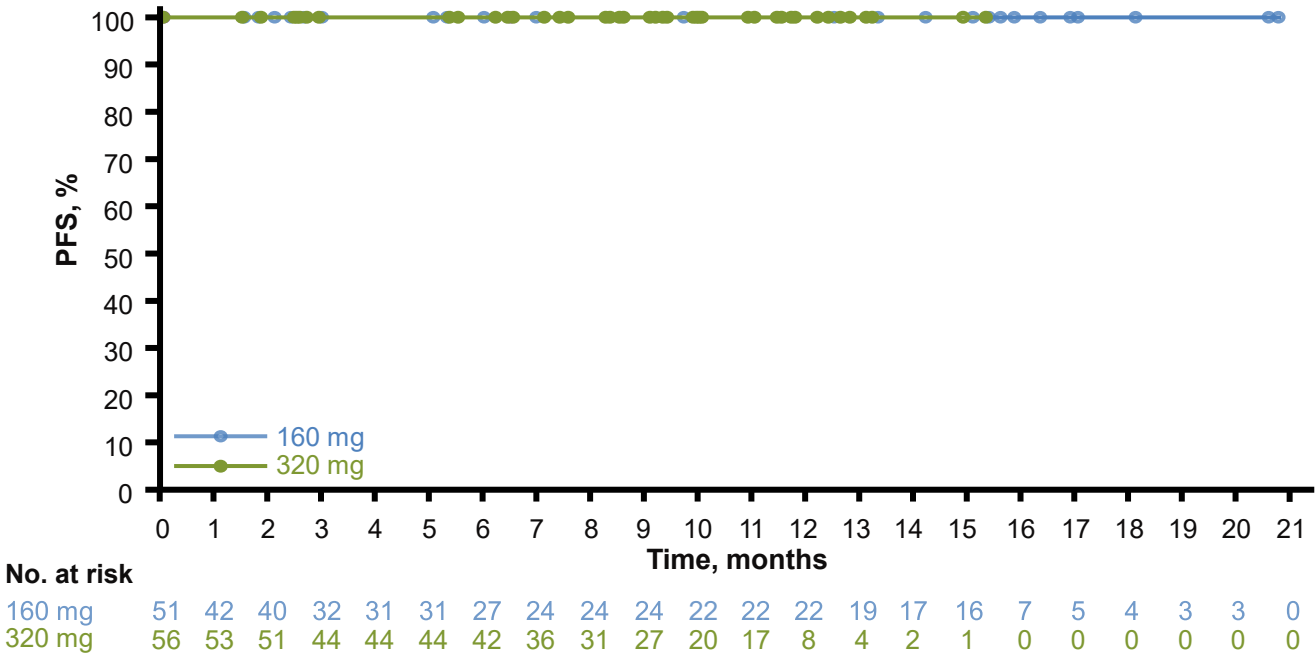
- High uMRD achieved at both dose levels
- Trend for higher uMRD rates with 320 mg
- Evidence of deepening response over time



^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-wk 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 wks 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 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
 - 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

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