Combination treatment with sonrotoclax (sonro; BGB-11417) + zanubrutinib (zanu) is well tolerated and achieves deep responses in patients with treatment-naive CLL/SLL: Data from an ongoing phase 1/2 study

Authors: P. Ghia[1|2], C.S. Tam[3], M.A. Anderson[4|5], M. Lasica[6], E. Verner[7|8], S. Opat[9], S. Ma[10], R. Weinkove[11|12], R. Cordoba[13], J. Soumerai[14], S. Leitch[15], J. Hilger[16], Y. Fang[17], D. Simpson[16], H. Guo[18], C.Y. Cheah[19|20|21]

Affiliations: [1]Università Vita-Salute San Raffaele; [2]IRCCS Ospedale San Raffaele; [3]Alfred Hospital and Monash University, Melbourne; [4]Royal Melbourne Hospital and Peter MacCallum Cancer Centre; [5]The Walter and Eliza Hall Institute; [6]St Vincent's Hospital Melbourne; [7]Concord Repatriation General Hospital; [8]University of Sydney; [9]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University; [10]Robert H. Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine; [11]Te Rerenga Ora Blood and Cancer Centre, Te Whatu Ora Health New Zealand Capital Coast & Hutt Valley; [12]Cancer Immunotherapy Programme, Malaghan Institute of Medical Research; [13]Hospital Universitario Fundación Jiménez Díaz; [14]Massachusetts General Hospital Cancer Center and Harvard Medical School; [15]Te Whatu Ora Health New Zealand – Waitemata; [16]BeiGene USA, Inc; [17]BeiGene (Beijing) Co, Ltd; [18]BeiGene (Shanghai) Co, Ltd; [19]Sir Charles Gairdner Hospital and PathWest Laboratory Medicine; [20]Medical School, University of Western Australia; [21]Linear Clinical Research

ABSTRACT

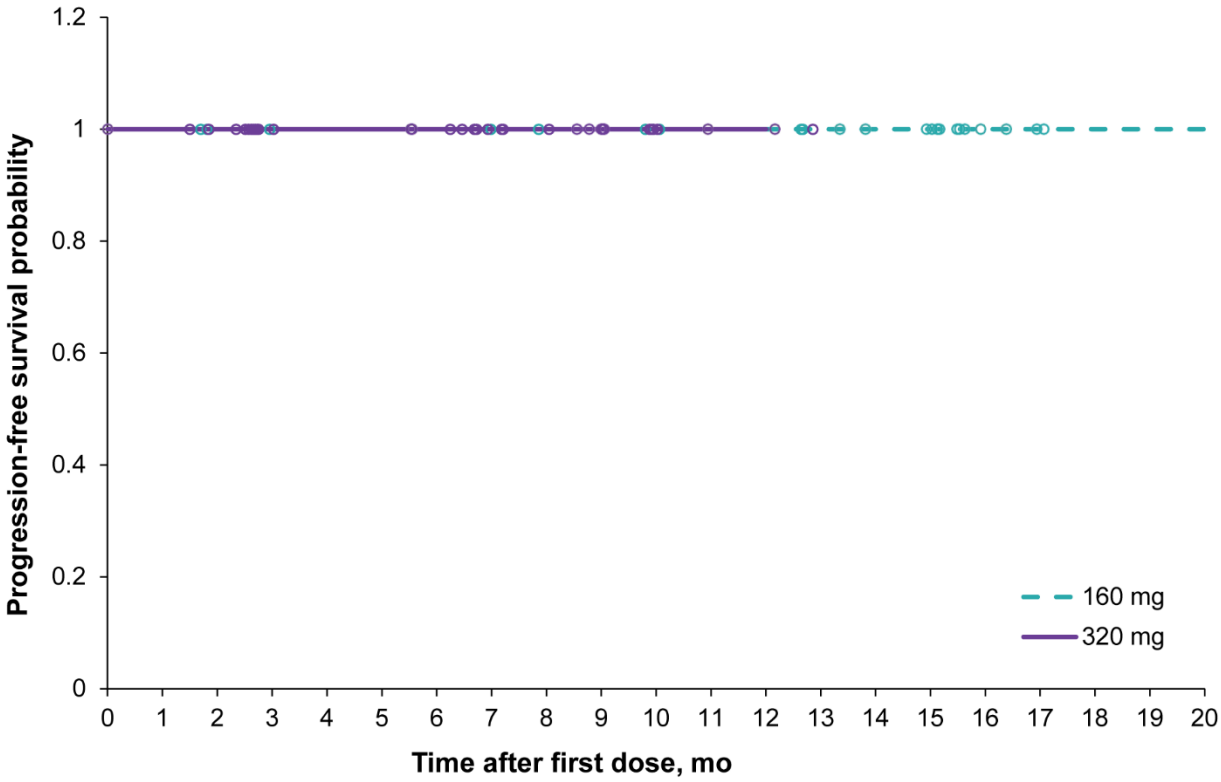
Background: Sonro (BGB-11417), a next-generation BCL2 inhibitor, is a more selective and potent inhibitor of BCL2 than venetoclax in biochemical assays. Zanu, a next-generation BTK inhibitor, improved PFS with fewer cardiac AEs than ibrutinib in patients (pts) with CLL/SLL. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, phase 1/1b dose-escalation/expansion study of pts with B-cell malignancies. Presented here are data from pts with treatment-naive (TN) CLL/SLL treated with sonro + zanu.

Methods: Pts received zanu (320 mg QD or 160 mg BID) 8 to 12 wk before starting sonro with a ramp-up schedule to target doses of 160 or 320 mg QD. Pts were treated until progression or unacceptable toxicity. TLS was assessed per Howard 2011 criteria. Safety per CTCAE v5.0 (primary endpoint [EP]), ORR per iwCLL 2008 criteria (secondary EP), and minimal residual disease (uMRD4) in blood by ERIC flow every 24 wk (exploratory EP) were assessed.

Results: As of May 21, 2023, 94 pts with TN CLL/SLL were enrolled; 15 pts were still in zanu lead-in and 79 had started sonro (160 mg, n=32; 320 mg, n=47). Median follow-up was 8.5 mo (range, 0.6-18.2) for all pts, 12.1 mo (range, 0.6-18.2) for 160 mg, and 7.0 mo (range, 1.1-14.6) for 320 mg. No deaths occurred, and all pts remain on study. TEAEs in ≥20% of pts who received sonro + zanu were contusion (35%), neutropenia (35%), COVID-19 (23%), and diarrhea (23%; grade ≥3 in 1 pt). Neutropenia was the most common grade ≥3 TEAE (17%). No clinical or laboratory TLS occurred. No pts experienced atrial fibrillation. One TEAE (cryptococcal meningitis at 11 wk) led to treatment discontinuation. Sonro dose holds occurred in 17 pts (22%; median duration, 11 days [range, 3-37]); 3 pts (4%) had dose reduction. In 56 response-evaluable pts, ORR was 100% (CR: 160 mg, 36% [n=9]; 320 mg, 19% [n=6]). CR rate increased with time; the median time to CR was 10.1 mo (range, 5.4-17.1). No progression events were reported in either cohort (**Figure**). Wk 24 blood uMRD4 rates were 50% (12/24) for 160 mg and 65% (13/20) for 320 mg. Wk 48 blood uMRD4 rates were 73% for 160 mg (11/15) and 100% (1/1) for 320 mg.

Conclusions: Sonro (160 and 320 mg) + zanu was well tolerated in pts with TN CLL/SLL. Only 1 pt discontinued treatment and 3 had dose reductions. No TLS was seen. Efficacy is encouraging, with 100% ORR in assessed pts, no PFS events, and high rates of blood uMRD4 occurring early. A phase 3 study assessing this combination is planned.

Figure: Progression-Free Survival With BGB-11417 + Zanubrutinib in Patients With TN-CLL by Dose



No. of patients at risk:

160 mg	41	29	27	26	25	25	25	24	22	22	19	18	18	15	13	12	3	1	0	0	0
320 mg	53	42	39	31	30	30	28	22	19	15	4	2	2	0	0	0	0	0	0	0	0