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

Authors: Constantine S. Tam,[1] Mary Ann Anderson,[2,3] Masa Lasica,[4] Emma Verner,[5,6] Stephen Opat,[7] Shuo Ma,[8] Robert Weinkove,[9,10] Raul Cordoba,[11] Jacob Soumerai,[12] Paolo Ghia,[13,14] Sophie Leitch,[15] James Hilger,[16] Yiqian Fang,[17] David Simpson,[16] Haiyi Guo,[18] Chan Y. Cheah[19,20,21]

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

ABSTRACT

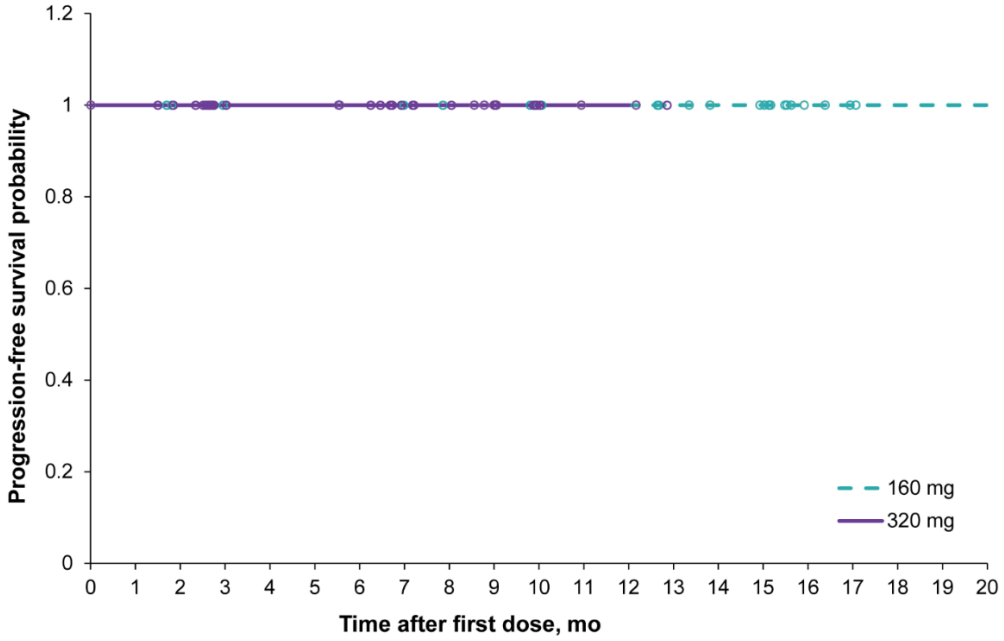
Aim: Sonrotoclax (BGB-11417), a next-generation BCL2 inhibitor, is more selective and potent than venetoclax in biochemical assays. Zanubrutinib, a next-generation BTK inhibitor, improved PFS with fewer cardiac AEs than ibrutinib in patients with CLL/SLL. BGB-11417-101 (NCT04277637) is an ongoing, first-in-human, dose-escalation/expansion study of sonrotoclax + zanubrutinib for B-cell malignancies. Data from patients with TN CLL/SLL are presented.

Method: Patients received zanubrutinib (320mg QD/160mg BID) 8-12 weeks before sonrotoclax target dose (160mg/320mg QD) ramp-up. TLS was assessed per Howard 2011 criteria. Endpoints included safety (CTCAEv5.0), ORR (iwCLL 2008 criteria), and minimal residual disease (uMRD4) in blood.

Results: As of 21May2023, 94 patients were enrolled; 15 were still in zanubrutinib lead-in and 79 started sonrotoclax (160mg, n=32; 320mg, n=47). Overall, median follow-up was 8.5 months. No deaths occurred; all patients remain on study. TEAEs in ≥20% of patients who received sonrotoclax + zanubrutinib were contusion (35%), neutropenia (35%), COVID-19 (23%), and diarrhea (23%; grade ≥3, n=1). Neutropenia was the most common grade ≥3 TEAE (17%). No TLS or atrial fibrillation occurred. One TEAE (cryptococcal meningitis) led to treatment discontinuation. Sonrotoclax dose holds occurred in 17 patients; 3 patients had dose reduction. In 56 response-evaluable patients, ORR was 100% (CR: 160mg, 36%; 320mg, 19%). CR rate increased with time; median time to CR was 10.1 months. No progression events were reported (Figure). Week 24 blood uMRD4 rates were 50% (160mg) and 65% (320mg). Week 48 blood uMRD4 rates were 73% (160mg) and 100% (320mg).

Conclusion: Sonrotoclax (160mg/320mg) + zanubrutinib was well tolerated in patients with TN CLL/SLL. Only 1 treatment discontinuation and 3 dose reductions occurred. No TLS was seen. Efficacy is encouraging, with 100% ORR in assessed patients, no PFS events, and high blood uMRD4 rates 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