Combination treatment with novel BCL2 inhibitor sonrotoclax (BGB-11417) + zanubrutinib induces high rate of complete remission in relapsed/refractory mantle cell lymphoma

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ABSTRACT

Introduction: Sonrotoclax (sonro; BGB-11417), a next-generation BCL2 inhibitor, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax. Zanubrutinib (zanu), a next-generation BTK inhibitor (BTKi), has favorable safety and efficacy, and is approved for relapsed/refractory (R/R) mantle cell lymphoma (MCL). Here, updated safety and efficacy data of sonro + zanu in patients (pts) with R/R MCL in the ongoing BGB-11417-101 (NCT04277637) study are reported.

Methods: Pts with R/R MCL (≥1 prior treatment [tx]) received zanu (320mg QD or 160mg BID) 8-12 wk before sonro (80, 160, 320, or 640mg QD) until progressive disease (PD) or unacceptable toxicity, with ramp-up to the target dose to mitigate tumor lysis syndrome (TLS) risk. Dose expansion occurred at 160 and 320mg. The primary endpoint was safety (CTCAE v5.0); a secondary endpoint was overall response rate (ORR) per 2014 Lugano classification. TLS was assessed per Howard 2011 criteria.

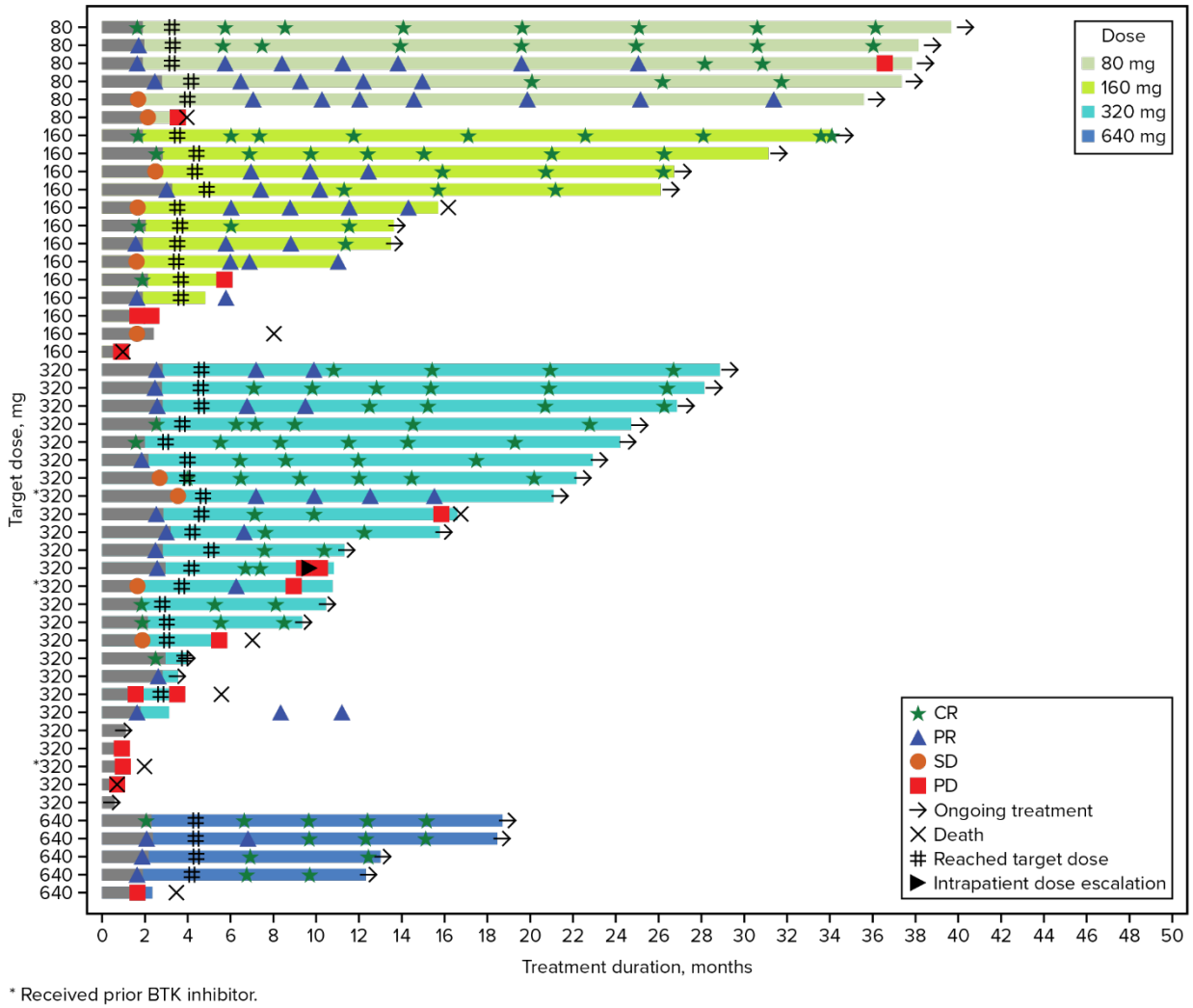
Results: As of December 6, 2024, 49 pts with R/R MCL were enrolled and treated (sonro doses: 80mg, n=6; 160mg, n=13; 320mg, n=25; 640mg, n=5): 7 were in the zanu lead-in phase, and 42 had started sonro. Median age was 68 y (range, 45-85), and 34 pts (69.4%) were male. Pts had a median of 1 prior tx (range, 1-4); 15 had prior stem cell transplant (1 allogeneic, 14 autologous), 1 had prior CAR T-cell therapy, and 3 had a prior BTKi. Median follow-up was 16.2 mo (range, 0.6-39.7). MTD was not reached up to sonro 640mg; 320mg was chosen as the RP2D. Twenty pts (40.8%) discontinued ≥1 study drug: 7 discontinued zanu only (PD, n=5 during zanu lead-in; AE, n=2 [diarrhea, meningitis; n=1 each]); 13 discontinued sonro + zanu (PD, n=8; AE, n=4 [myelodysplastic syndromes, pneumonia, diarrhea, abdominal sepsis; n=1 each]; pt withdrawal, n=1). Eight pts died due to PD (4 during zanu lead-in). Tx-emergent AEs (TEAEs) in ≥30% of pts were contusion, COVID-19, diarrhea, and neutropenia (30.6%

each). The most common grade ≥3 TEAE was neutropenia (20.4%). No laboratory or clinical TLS occurred. No atrial fibrillation/flutter or ventricular arrhythmia was reported. TEAEs led to death in 2 pts (4.1%; pneumonia, n=1; abdominal sepsis [not tx-related], n=1). In 45 response-evaluable pts across doses, ORR was 77.8% (n=35); complete response (CR) rate was 62.2% (n=28) (**Figure**). Median time to CR was 6.7 mo; 89% of pts (25/28) remained in CR at data cutoff. In the 160-mg and 320-mg expansion cohorts (median follow-up, 16.2 and 12.9 mo, respectively), CR rate was 53.8% (7/13) and 61.9% (13/21) and ORR was 76.9% (10/13) and 76.2% (16/21), respectively. Of 3 response-evaluable pts with prior BTKi tx, 2 had partial responses and 1 had PD.

Conclusions: Sonro + zanu combination tx was well tolerated and demonstrated encouraging antitumor activity, with a CR rate of 62.2%, and responses in pts with prior BTKi tx. A registrational phase 3 study (NCT06742996) further assessing this combination with sonro 320mg is recruiting.

Figure/Table/Image:

Figure. Swimlane plot of investigator-assessed responses in all patients



* Received prior BTK inhibitor.