Combination Treatment With Novel BCL2 Inhibitor Sonrotoclax (BGB-11417) and Zanubrutinib Induces High Rate of Complete Remission for Patients With Relapsed/Refractory Mantle Cell Lymphoma

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Background: Mantle cell lymphoma (MCL) is a rare, incurable subtype of B-cell NHL, characterized by continuous relapses after initial therapy. The phase 3 SYMPATICO study showed that combination therapy with venetoclax, a BCL2 inhibitor (BCL2i), and ibrutinib, a Bruton tyrosine kinase inhibitor (BTKi), had efficacy in patients (pts) with relapsed/refractory (R/R) MCL; however, treatment intolerance may impact its use. Sonrotoclax (BGB-11417), a next-generation BCL2i, is a more selective and pharmacologically potent inhibitor of BCL2 than venetoclax, with a shorter half-life and no drug accumulation. Zanubrutinib (zanu), a next-generation BTKi, has favorable safety and efficacy, and is approved for R/R MCL.

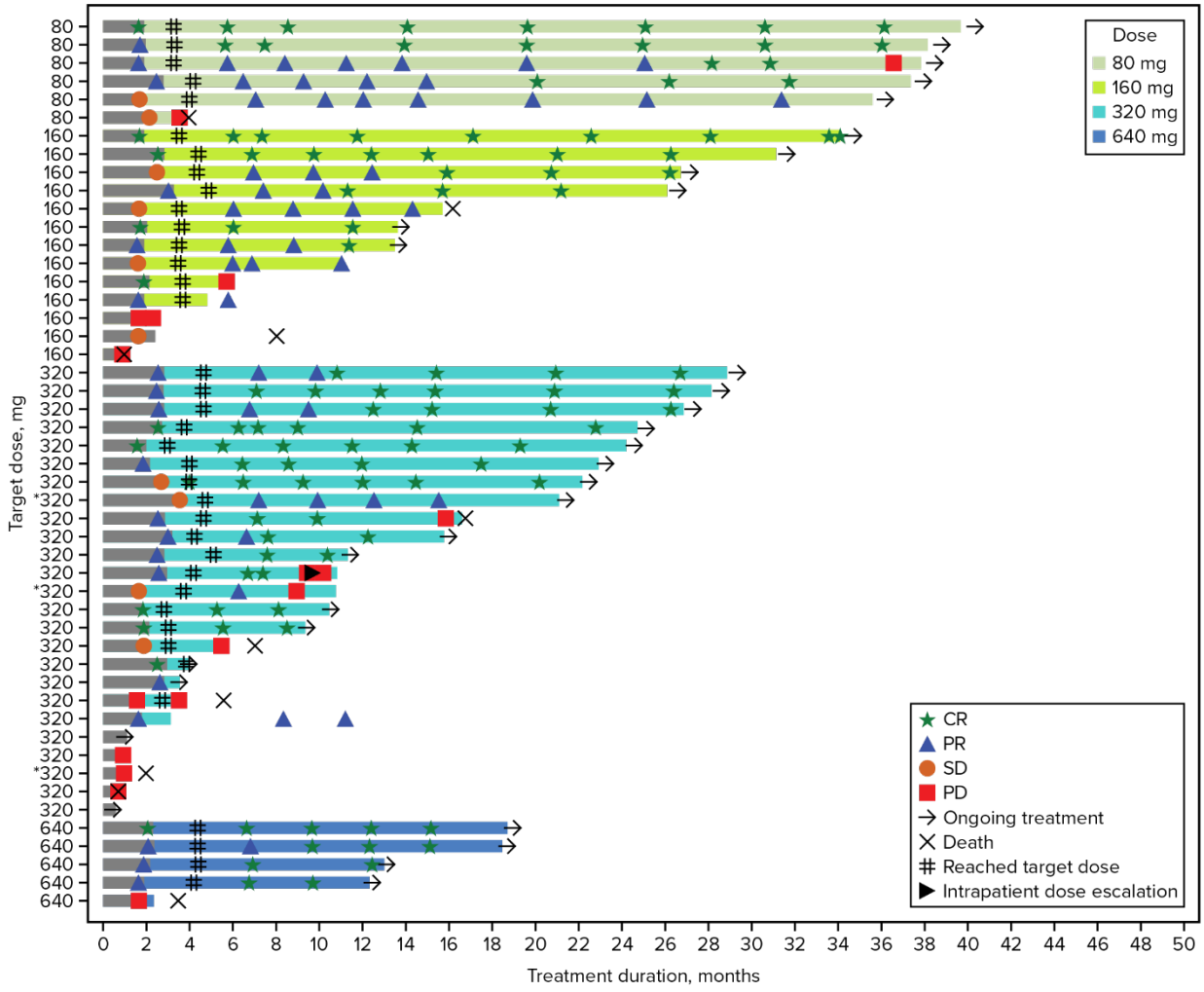
Aims: To report updated safety and efficacy data for pts with R/R MCL treated with sonrotoclax + zanu in the ongoing BGB-11417-101 (NCT04277637) study.

Methods: Pts with R/R MCL (≥1 prior therapy) received zanu (320mg QD or 160mg BID) 8-12 wk before sonrotoclax (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 had received combination therapy (sonrotoclax doses: 80mg, n=6; 160mg, n=13; 320mg, n=25; 640mg, n=5). Seven pts were in the zanu lead-in phase; 42 had started sonrotoclax. Median age was 68 y (range, 45-85), and 34 pts (69.4%) were male. The median number of prior therapies was 1 (range, 1-4); 15 pts had a 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). Maximum tolerated dose was not reached up to sonrotoclax 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 combination therapy (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). Treatment-emergent AEs (TEAEs) observed 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 events of atrial fibrillation/flutter or ventricular arrhythmia were reported. TEAEs led to death in 2 pts (4.1%; pneumonia, n=1; abdominal sepsis [not treatment-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**). The 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 therapy, 2 partial responses and 1 PD were observed.

Summary/Conclusion: Sonrotoclax + zanu combination therapy was well tolerated and demonstrated encouraging antitumor activity, with a CR rate of 62.2%, and responses in pts previously treated with a BTKi. A registrational phase 3 study (NCT06742996) further assessing this combination with sonrotoclax 320mg is recruiting.

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



* Received prior BTK inhibitor.