Sonrotoclax plus dexamethasone is tolerable and demonstrates antimyeloma activity in patients with relapsed/refractory (R/R) multiple myeloma harboring t(11;14)

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Background: BCL2 is an attractive therapeutic target in multiple myeloma (MM) with t(11;14), in that MM cells are primed for BCL2 and responsive to oral BCL2 inhibitors, such as venetoclax, a first-generation BCL2 inhibitor. Although BCL2 inhibitors have shown clinical activity in patients (pts) with MM, no BCL2-targeted therapies are currently approved for MM. Sonrotoclax (BGB-11417) is more selective and a more pharmacologically potent inhibitor of BCL2 than venetoclax in biochemical assays. BGB-11417-105 (NCT04973605) is an ongoing, phase 1b/2 trial evaluating the safety and efficacy of sonrotoclax as monotherapy or as combination therapy for pts with R/R MM harboring t(11;14).

Aims: To report updated safety and efficacy data from the sonrotoclax plus dexamethasone cohort in pts with R/R MM treated with 640 mg sonrotoclax.

Methods: Eligible pts have R/R MM harboring centrally-confirmed t(11;14) and had received a minimum of 3 (dose–finding cohort) or 1 (dose–expansion cohort) prior line(s) of therapy. Pts received 640 mg sonrotoclax orally, once daily, and 40 mg dexamethasone weekly until intolerance, disease progression, consent withdrawal, or death. Adverse events (AEs) were graded per CTCAE v5.0 and disease responses were assessed by the investigator per the International Myeloma Working Group response criteria (Kumar et al, 2016).

Results: As of Jan 8, 2024, 20 pts had been enrolled in the 640 mg dose-escalation (n=10) and dose-expansion (n=10) cohorts with a median follow-up of 6.2 months (range, 0.3-16.6 months). Median age was 70 yrs (range, 48-79 yrs); 50% were male, 85% were White, 5% were Black, and 5% were Hispanic. The median number of prior lines of therapy was 4 (range, 1-12), with 70% and 80% of pts refractory to anti-CD38 therapy and IMiDs, respectively. At the data cutoff, 13 pts (65%) were still on study treatment (reasons for discontinuation: disease progression [n=3], AE [n=2; hematuria, pancreatic cancer], pt withdrawal [n=1], and physician decision [n=1]). Nineteen (95%) pts experienced a treatment-emergent AE (TEAE); insomnia (n=6; 30%), diarrhea, fatigue, and nausea (each n=5; 25%) were the most common. Hematologic TEAEs occurred in 3 pts (thrombocytopenia [n=2; grades 1 and 3], neutropenia [n=1; grade 1]). Serious TEAEs occurred in 3 pts (15%) and grade ≥3 AEs occurred in 4 pts (20%); none were considered related to sonrotoclax (2 pts experienced both serious TEAEs and grade ≥3 TEAEs). No pt experienced a dose-limiting toxicity. Two pts died on study; both deaths were not considered related to study therapy (1 TEAE [metastatic pancreatic cancer] and 1 non-TEAE [liver failure due to hepatocellular carcinoma]). Infections that were observed in >1 pt were COVID-19 (n=2; 10%) and upper respiratory tract infection (n=2; 10%). Among 15 efficacy-evaluable pts, the ORR was 80% (n=12; 95% CI, 51.9-95.7), with a 40% VGPR or better rate (n=6). The median time to response was 0.7 months and median duration of response (DOR) was 8.3 months (95% CI, 4.4 to not reached) with a maximum DOR of 15.4 months (ongoing; Figure).

Summary/Conclusion: With longer follow-up, sonrotoclax plus dexamethasone continues to demonstrate a manageable safety profile, with low rates of hematologic toxicities and infections. The combination provided deep and durable responses in this R/R population. The study is ongoing, and other combination treatments with sonrotoclax are being investigated.

Figure. Treatment duration and response assessment in patients with R/R MM harboring t(11;14)