Sonrotoclax (BGB-11417) in Combination With Dexamethasone for the Treatment of Relapsed/Refractory Multiple Myeloma With t(11;14): Safety, Efficacy, and Determination of Recommended Phase 2 Dose

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ABSTRACT

Background: B-cell lymphoma-2 (BCL2) family proteins represent attractive therapeutic targets as they play an important role in MM cell survival. In patients with relapsed/refractory (R/R) MM harboring t(11;14) for whom multiple prior lines of therapy failed, single-agent venetoclax, a first generation BCL2 inhibitor, demonstrated antimyeloma activity (Kumar S, et al. *Blood.* 2017). Dexamethasone, a long-standing mainstay of treatment for MM, increases the expression of both BCL2 and Bim. This results in a greater dependency on BCL2 for tumor survival, ultimately increasing the sensitivity to a BCL2 inhibitor.

Sonrotoclax (BGB-11417) is a BH3 mimetic that binds and inhibits BCL2 with potency >10x that of venetoclax in biochemical assays. BGB-11417-105 (NCT04973605) is an ongoing phase 1b/2 trial designed to evaluate safety and efficacy of sonrotoclax as monotherapy, in combination with dexamethasone, or in combination with dexamethasone plus carfilzomib in patients with R/R MM harboring the t(11;14) . Here, we report preliminary data from the sonrotoclax plus dexamethasone dose-escalation (DE) cohorts.

Methods: Eligible patients have R/R MM that is t(11;14) positive by fluorescence in situ hybridization (per central assessment) who have received 1-7 prior lines of therapy for MM with previous exposure to a proteasome inhibitor and an IMiD agent. In dose escalation, patients received 80, 160, 320, or 640 mg of sonrotoclax daily with 40 mg of dexamethasone weekly until intolerability, disease progression, or death. The primary objectives in the DE cohorts were to assess the overall safety/tolerability profile as well as determine the maximum tolerated dose (MTD)/maximum assessed dose (MAD) and establish the recommended phase 2 dose (RP2D). AEs were reported per CTCAEs v5.0; safety was assessed by a safety monitoring committee (SMC) after a 21-day dose-limiting toxicity (DLT) window for each cohort and was guided by a modified toxicity probability interval method (mTPI-2). Disease responses were assessed per International Myeloma Working Group 2016 criteria.

Results: As of May 26, 2023, 19 patients have been enrolled in the 80-, 160-, and 320-mg (n=3 each) and 640-mg (n=10 patients) dose-escalation cohorts. The median age was 68 years (range, 52-81 years). The median prior lines of therapy was 4 (range, 1-12) and 11 patients (58%) failed on a prior anti-CD38 antibody. The most common AEs

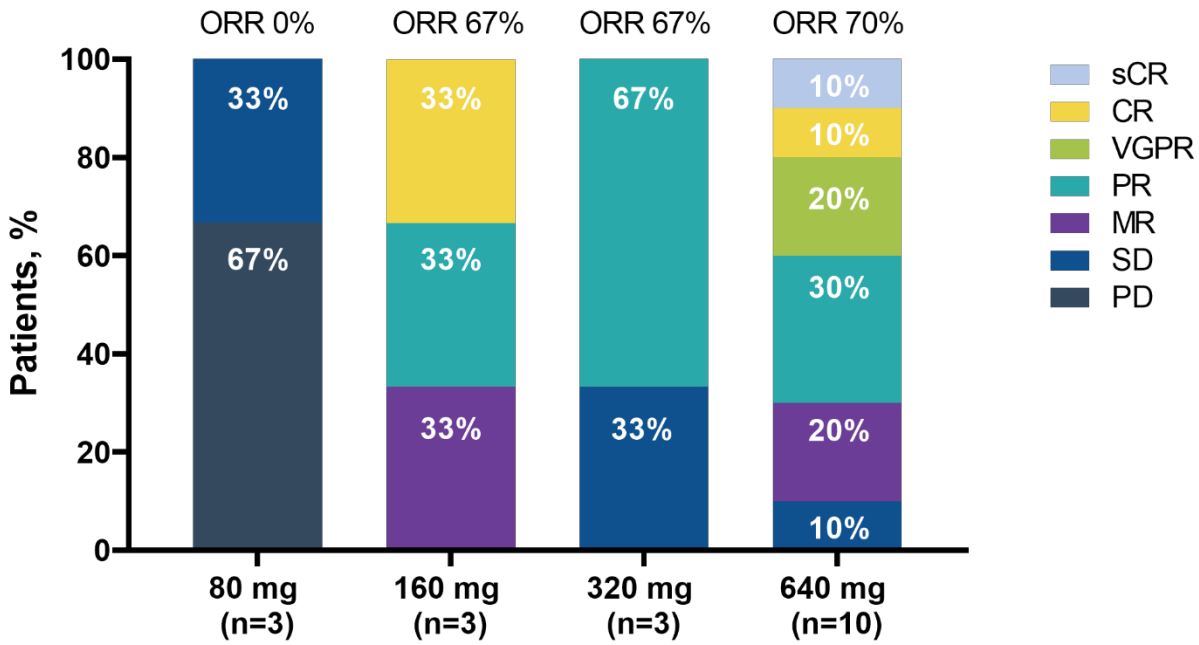
(>20% of all patients) were insomnia (n=9; 47%), fatigue (n=6; 32%), nausea (n=5; 26%), and arthralgia (n=4; 21%); none of which were severity grade ≥3. Three patients (16%) experienced grade ≥3 treatment-emergent AEs (TEAEs). One patient (33%) in the 160-mg cohort had grade 3 increases in liver enzymes and diarrhea; one patient (10%) in the 640-mg cohort had a grade 3 decrease lymphocyte count and hypokalemia; and one patient (10%) in the 640-mg cohort had grade 3 cataracts and retinal detachment. Three patients experienced COVID-19 (grade 1-2, n=2; grade ≥3, n=1). Three patients experienced TEAEs that led to treatment discontinuation (COVID-19, cancer pain, hematuria; n=1 each). No patient, across all dose levels tested, experienced a DLTs; thus, sonrotoclax 640 mg daily was the determined to be the MAD and the RP2D in combination with dexamethasone.

Four patients (21%) died while on study; however, no deaths were determined by the investigators to be associated with study treatment. One patient died from COVID-19 while receiving study therapy; three additional patients died ≥50 days after treatment discontinuation (COVID, progressive disease, and unknown causes, n=1 each).

With a median treatment duration of 120 days (range, 30-526), ORR was 58%; 11 patients had a PR or better (n=6, PR; n=2, very good PR; n=2, CR; n=1, stringent CR [sCR]; Figure). The ORR for the 640-mg cohort was 70% (n=3, PR; n=2 VGPR; n=1, CR; n=1, sCR). Nine patients remained on treatment; the longest duration of response was 483 days (20 cycles) which, at data cutoff, was still ongoing.

Conclusion: Sonrotoclax plus dexamethasone was generally well tolerated in patients with R/R MM harboring t(11;14) at doses up to 640 mg, and initial safety and efficacy results are promising. The SMC has recommended 640 mg in combination with dexamethasone as the RP2D. Recruitment is ongoing for the sonrotoclax in combination with dexamethasone and carfilzomib dose-finding arms and the sonrotoclax plus dexamethasone indication expansion cohort.

Figure: Best Overall Response by Dose Level



CR, complete response; MR, minimal response; ORR, overall response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.