Preliminary Safety and Efficacy of BGB-11417 (Novel Bcl-2 Inhibitor) in Combination With Azacitidine in AML

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Background

BGB-11417 is a potent Bcl-2 inhibitor (>10-fold versus venetoclax in biochemical assays) with improved selectivity and the potential to achieve deeper target inhibition and responses in the clinical setting. Updated preliminary results for BGB-11417+azacitidine in AML are presented.

Methods

BGB-11417-103 (NCT04771130) is an ongoing dose-finding/expansion study. Eligible patients with treatment-naive (TN) AML (unfit for intensive chemotherapy) or

relapsed/refractory (R/R) AML received 40mg (cohort 1), 80mg (cohort 2), or 160mg (cohort 3) BGB-11417 x 10days or 160mg x 28days (cohort 4). All doses were given with 75mg/m^2 azacitidine x 7days. Responses were determined per 2017 European LeukemiaNet (ELN) criteria. Dose-limiting toxicities (DLT), treatment-emergent adverse events (TEAEs) and minimal residual disease (MRD) were assessed.

Results

By June 1, 2022, 51 patients with AML were treated (cohort 1=16; cohort 2=17; cohort 3=14; cohort 4=4). Median age was 77years (TN=28) and 64years (R/R=23). At baseline, 23 patients (45.1%) had adverse-risk cytogenetics, 37 (72.5%) had grade ≥3 neutropenia, and 27 (52.9%) had grade ≥3 thrombocytopenia.

At a median follow-up of 2.8months (range 0.1-12.3) and median treatment duration of 1.9months (range 0.0-12.3), 2/41 evaluable patients had DLTs (grade 4 neutropenia and thrombocytopenia, both at 80mg); stopping criteria was not met. One patient (160mg x 10days) had laboratory tumor lysis syndrome per Howard criteria that resolved in 4days. Twenty-one patients (41%) discontinued treatment: AEs=7(13.7%); disease progression=5(9.8%); went to transplant=4(7.8%); withdrew consent=3(5.9%); investigator decision=1(2.0%); started new anticancer treatment=1(2.0%). The most common TEAEs were neutropenia (58.8%), thrombocytopenia (45.1%), anemia (43.1%), nausea (39.2%), and constipation (37.3%). Neutropenia was the most common grade ≥3 TEAE seen in 30 patients (58.8%); most did not require dose modification. Grade ≥3 infections occurred in 23 patients (45.1%). Four patients (7.8%) died due to unrelated TEAEs. TEAEs leading to dose reduction (5.9%) or interruption (11.8%) were infrequent. In TN AML, complete remission (CR)/CR with partial hematologic recovery (CRh) was achieved in 16 patients (59.3%) and CR in 13 evaluable patients (48.1%). Of the 13 patients in CR, 7(53.8%) reached CR by the end of cycle 1. In R/R AML, CR/CRh was seen in 50% of evaluable patients, with a CR rate of 25%; 9/18 evaluable patients (50.0%; TN=6, R/R=3) with CR/CRh achieved MRD negativity (<0.1% per ELN 2018).

Conclusion

These results demonstrate that BGB-11417+azacitidine was effective and generally well tolerated at the 4 dose levels tested in AML, with no dose-dependent toxicity observed. Further dose escalation is underway.