Preliminary Safety of Bcl-2 inhibitor BGB-11417 in Relapsed/Refractory Multiple Myeloma Harboring t(11,14): Phase 1b/2 Study

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ABSTRACT

Background

B-cell lymphoma-2 (Bcl-2) proteins play an important role in multiple myeloma (MM) cell survival and represent an attractive therapeutic target. In prior trials, a subgroup analysis of patients with t(11;14)-positive relapsed/refractory (R/R) MM showed the combination of a Bcl-2 inhibitor, a proteasome inhibitor, and dexamethasone improved progression free survival with no increased mortality. BGB-11417, a Bcl-2 inhibitor, is more potent and selective than venetoclax. BGB-11417-105 (NCT04973605) is a phase 1b/2 study assessing the safety and efficacy of BGB-11417 monotherapy, in combination with dexamethasone, or with dexamethasone+carfilzomib in patients with t(11;14)-positive R/R MM. Preliminary safety results for the combination of BGB-11417+dexamethasone are presented.

Methods

Eligible patients had t(11;14)-positive R/R MM and had been exposed to a proteasome inhibitor, immunomodulatory agent, and anti-CD38 therapy. Patients received 80-, 160-, 320-, or 640-mg BGB-11417 daily with 40-mg dexamethasone weekly until death, intolerability, or disease progression. Dose escalation was guided by a mTPI-2 design and overall review by a safety monitoring committee. Pharmacokinetics (PK) were also assessed.

Results

As of July 1, 2022, 10 patients were enrolled in the 80-, 160-, and 320-mg (3 patients each) and 640-mg (1 patient) dose-escalation cohorts of BGB-11417+dexamethasone. The median age was 69 years (range, 52-81) and median prior lines of therapy was 3 (range, 1-5). The median treatment duration was 3.2 months (range, 0.5-6.5). No patients experienced dose-limiting toxicity at any dose level. Three patients died while on study: 1 due to COVID-19 complications 157 days after treatment discontinuation (day 208), 1 due to progressive disease 50 days after treatment discontinuation (day 89), and 1 due to COVID-19 while on study treatment (day 78). No deaths were associated with study treatment. Two patients experienced Grade ≥3 treatment-emergent adverse events (TEAEs). One patient in the 160-mg cohort experienced Grade 3 increase in liver enzymes and lymphopenia. One patient in the 320-mg cohort experienced Grade 3 lymphopenia. The most common TEAEs were insomnia (50%), fatigue (30%), arthralgia (20%), back pain (20%), lymphopenia (20%), and nausea (20%). BGB-11417 exposure increased dose-dependently from 80 mg to 320 mg with high interpatient PK variability. BGB-11417 exposures after single and multiple doses appeared similar, indicating limited accumulation.

Conclusion

BGB-11417 plus dexamethasone was generally well tolerated in patients with R/R MM harboring t(11;14) at doses ≤640 mg. Efficacy data are forthcoming. Recruitment is ongoing in the US, Australia, and New Zealand; the BGB-11417, dexamethasone, and carfilzomib combination arm will open in the future.