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. Multiple studies suggest that patients (pts) with t(11;14)-positive relapsed/refractory (RR) MM respond well to Bcl-2 inhibition and show improved progression free survival. BGB-11417 is a potent and highly selective Bcl-2 inhibitor. BGB-11417-105 (NCT04973605) is a phase 1b/2 study assessing the safety and efficacy of BGB-11417 monotherapy, and in combination with dexamethasone, or carfilzomib and dexamethasone in pts with t(11;14)-positive RR MM. Preliminary safety results for BGB-11417 with dexamethasone are presented.

Materials and Methods

Pts had t(11;14)-positive RR MM and had previously received a proteasome inhibitor, immunomodulatory agent, and anti-CD38 therapy. Pts received 80, 160, 320, or 640mg BGB-11417 daily with 40mg dexamethasone weekly until death, intolerability, or progressive disease (PD). An mTPI-2 design and overall review by a safety monitoring committee guided dose escalation. Pharmacokinetics (PK) were also assessed.

Results

As of July 1, 2022, 10 pts were enrolled in the 80, 160, and 320mg (3 pts each) and 640mg (1 pt) dose-escalation cohorts of BGB-11417+dexamethasone. Median age: 69 (range, 52-81); median prior lines of therapy: 3 (range, 1-5); median treatment duration: 3.2 mo (range, 0.5-6.5). No pts reached dose-limiting toxicity. Three pts died: 1 due to COVID-19 complications 157 d after treatment discontinuation (d 208), 1 due to PD 50 d after treatment discontinuation (d 89), and 1 due to COVID-19 while on study treatment (d 78). No treatment-associated deaths occurred. Two pts had Grade≥3 treatment-emergent adverse events (TEAEs). One pt in the 160mg cohort had Grade 3 increase in liver enzymes and lymphopenia and1 pt in the 320mg cohort had 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 80mg to 320mg with high interpatient PK variability. BGB-11417 exposures after single and multiple doses appeared similar, indicating limited accumulation.

Conclusion

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