Preliminary Safety of a Bcl-2 Inhibitor, BGB-11417, in Patients With Relapsed/Refractory Multiple Myeloma Harboring t(11,14): A Non-randomized, Open-label, Phase 1b/2 Study

Authors: Hang Quach,[1] Rajeev Rajagopal,[2] Andrew Spencer,[3] Michael Low,[4] Dickran Kazandijan,[5] Rocco Crescenzo,[6] Chenmu Du,[6] Sheel Patel,[6] Vaibhav Mundra,[6] Huan Cheng,[6] and Binod Dhakal[7]

Affiliations: *[1]St. Vincents Hospital Melbourne, University of Melbourne, Melbourne, Victoria, Australia; [2]Middlemore Hospital, Auckland, New Zealand; [3] The Alfred Hospital, Melbourne, Victoria, Australia; [4]Monash Health, Melbourne, Victoria, Australia; [5]Sylvester Comprehensive Cancer Center, Miami, Florida, USA; [6]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; and [7]Medical College of Wisconsin, Milwaukee, Wisconsin, USA*

Background/Introduction: The family of B-cell lymphoma-2 (Bcl-2) proteins plays an important role in multiple myeloma (MM) cell survival and represents an attractive therapeutic target. In prior trials, the combination of a Bcl-2 inhibitor, a proteasome inhibitor, and dexamethasone, showed increased mortality in the ITT population, but a subgroup analysis of patients with t(11;14) positive R/R MM showed an improved progression free survival, with no increased mortality. Compared to venetoclax, BGB-11417 is a more potent (>10 fold in biochemical assays) and highly selective Bcl-2 inhibitor.

The ongoing BGB-11417-105 trial (NCT04973605) is a phase 1b/2 study determining the safety and efficacy of BGB-11417 as monotherapy, in combination with dexamethasone, or with dexamethasone plus carfilzomib in patients with t(11;14) positive R/R MM. Here, we present preliminary safety results for the combination of BGB-11417 and dexamethasone from study BGB-11417-105.

Methods: Eligible patients with t(11;14) positive R/R MM who had been exposed to a proteasome inhibitor, immunomodulatory agent, and an anti-CD38 therapy were included. Patients received 80, 160, 320, or 640 mg of BGB-11417 daily with 40 mg of dexamethasone weekly until death, intolerability, or disease progression. Adverse events (AEs) were reported per Common Terminology Criteria for AEs v5.0. Dose escalation (after a 21-day dose-limiting toxicity window) was guided by a mTPI-2 design and overall review by a safety monitoring committee. Pharmacokinetics (PK) was also assessed.

Results: As of the data cutoff date, July 1, 2022, a total of 10 patients have been enrolled in the 80, 160, and 320 mg (3 patients each) and 640 mg (1 patient) dose-escalation cohorts of BGB-11417 plus dexamethasone. The median age of all patients enrolled in the trial was 69 years (range, 52-81), median prior lines of therapy was 3 (range, 1-5), 7 patients had an ECOG performance score of 0, and 3 patients had a ECOG score of 1. The median treatment duration was 3.2 months (range, 0.5-6.5). No patients experienced dose-limiting toxicity at any dose level tested. Three patients died while on study, 1 due to COVID-19 complications 157 days after treatment discontinuation on day 208 of the study, 1 due to progressive disease 50 days after treatment discontinuation on day 89 of the study, and 1 due to COVID-19 while on study treatment at day 78. All deaths were determined to not be associated with study treatment, by the investigator. Two other patients experienced grade ≥3 treatment-emergent AEs (TEAEs). One patient in the 160 mg cohort experienced a grade 3 increase in liver enzymes and lymphopenia. One patient in the 320 mg cohort experienced a grade 3 lymphopenia. The most common TEAEs were insomnia (50%), fatigue (30%), arthralgia (20%), back pain (20%), lymphopenia (20%), and nausea (20%). A summary of TEAEs observed for each dose level is shown in the **Table**.

BGB-11417 exposure increased in a dose-dependent manner from 80 mg to 320 mg with high inter-patient PK variability. BGB-11417 exposures after single and multiple doses appeared similar, indicating limited accumulation of BGB-11417.

Conclusion: BGB-11417 in combination with dexamethasone was generally well tolerated in patients with R/R MM harboring t(11;14) at doses up to 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.

Table: Overall Treatment-Emergent Adverse Events

TEAEs by preferred term[a]	BGB-11417 80 mg + dex (n=3)	BGB-11417 160 mg + dex (n=3)	BGB-11417 320 mg + dex (n=3)	BGB-11417 640 mg + dex (n=1)	Total (N=10)
Patients with ≥1 TEAE	3 (100)	3 (100)	3 (100)	0	9 (90.0)
Insomnia	1 (33.3)	2 (66.7)	2 (66.7)	0	5 (50.0)
Fatigue	1 (33.3)	0	2 (66.7)	0	3 (30.0)
Arthralgia	1 (33.3)	0	1 (33.3)	0	2 (20.0)
Back pain	0	1 (33.3)	1 (33.3)	0	2 (20.0)
Lymphocyte count decreased	0	1 (33.3)	1 (33.3)	0	2 (20.0)
Nausea	1 (33.3)	1 (33.3)	0	0	2 (20.0)
Agitation	1 (33.3)	0	0	0	1 (10.0)
Alopecia	0	1 (33.3)	0	0	1 (10.0)
Blepharospasm	0	0	1 (33.3)	0	1 (10.0)
COVID-19	0	0	1 (33.3)	0	1 (10.0)
Diarrhea	0	1 (33.3)	0	0	1 (10.0)
Dyspnea	0	0	1 (33.3)	0	1 (10.0)
Ear discomfort	0	1 (33.3)	0	0	1 (10.0)
Fluid retention	1 (33.3)	0	0	0	1 (10.0)
Gastroesophageal reflux disease	0	0	1 (33.3)	0	1 (10.0)
Hot flush	0	0	1 (33.3)	0	1 (10.0)
Liver function test increased	0	1 (33.3)	0	0	1 (10.0)
Myopathy	0	0	1 (33.3)	0	1 (10.0)
Neutropenia	0	0	1 (33.3)	0	1 (10.0)
Pruritus	0	0	1 (33.3)	0	1 (10.0)
Renal impairment	1 (33.3)	0	0	0	1 (10.0)
Rhinovirus infection	0	0	1 (33.3)	0	1 (10.0)
Vomiting	1 (33.3)	0	0	0	1 (10.0)

Dex, dexamethasone; TEAE, treatment-emergent adverse event.

Data cutoff: July 1, 2022. Data extraction: July 18, 2022.

[a]Patients with multiple events for a given preferred term are counted only once for each preferred term. Events are sorted by decreasing frequency of preferred term in the Total group, from the safety analysis set analyzed using MedDRA v25.0.