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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INTRODUCTION

- Patients harboring the t(11;14) translocation when treated with Bcl-2 inhibitors have better outcomes[1]
- BGB-11417 was developed as a potent and highly selective inhibitor of Bcl-2[2]
- Combining Bcl-2 inhibitor with dexamethasone or a proteasome inhibitor can improve clinical outcomes[3]
  - Dexamethasone shifts Bim binding to Bcl-2, resulting in an increased sensitivity to Bcl-2 inhibition[4]
  - A combination of Bcl-2 inhibitor with a proteasome inhibitor provides a synergistic effect causing cell death[4]
- In nonclinical studies, BGB-11417 has demonstrated better selectivity and potency compared with venetoclax alone, potentially leading to deeper responses and an improved safety profile[5]
- Here we present the dose escalation data for BGB-11417 in combination with dexamethasone from Part 1 of the BGB-11417-105 study in patients with R/R MM harboring t(11;14)

OBJECTIVES (PART 1)

Primary objective:

- Safety, tolerability, and RP2D of BGB-11417 in combination with dexamethasone with or without carfilzomib, MTD for BGB-11417 in combination with dexamethasone

Secondary objective:

- PK of BGB-11417 in combination with dexamethasone with or without carfilzomib

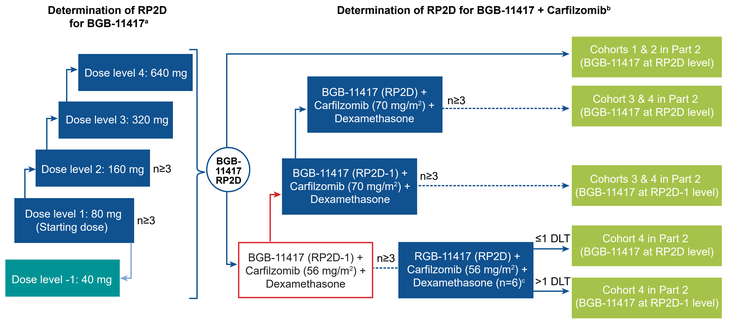
Exploratory objectives:

- ORR of BGB-11417 in combination with dexamethasone with or without carfilzomib, PK of dexamethasone in combination with BGB-11417

METHODS

- BGB-11417-105 is an open-label, multicenter, phase 1b/2 dose escalation study of BGB-11417 + dexamethasone and BGB-11417 + dexamethasone and carfilzomib in patients harboring t(11;14) R/R MM (**Figure 1**)
- Bone marrow t(11;14) status was centrally assessed at study entry using fluorescence in situ hybridization (Abbott Laboratories)
- Responses were assessed as per International Myeloma Working Group 2016 criteria
- AEs were reported per CTCAE v5.0
- Nonhematologic DLTs included grade ≥3 nonhematologic toxicity except alopecia and laboratory TLS or TLS-related laboratory AEs that resolved (grade ≤1 or baseline) in ≤3 days; asymptomatic biochemical laboratory abnormalities that resolved (grade ≤1 or baseline) in ≤7 days; grade 2 gastrointestinal toxicity (nausea, vomiting or diarrhea) unresponsive to treatment for ≥7 days; and grade 2 neuropathy with pain that did not resolve to grade ≤1 within 2 weeks
- Hematologic DLTs included grade ≥4 hematological toxicity, grade ≥3 febrile neutropenia or neutropenia lasting >7 days with GCS-F support, and grade ≥3 thrombocytopenia lasting >7 days or resulting in clinically significant bleeding
- Dose escalation (after a 21-day DLT window) was guided by an mTPI-2 design
- RP2D will be defined by reviewing the totality of safety, efficacy, and PK data in all tested cohorts

Figure 1. Study Design Part 1 Dose Escalation in Patients Harboring t(11;14) R/R MM



Dashed arrow indicated the dose combination of BGB-11417 + carfilzomib is selected as the combination MTD or MAD.
[a]BGB-11417 + dexamethasone (40 mg weekly); dose escalation guided by mTPI-2: target toxicity probability = 0.2, EI = (0.15, 0.25); maximum dose sample size = 18. [b]BGB-11417 + carfilzomib (56 mg/m² or 70 mg/m² weekly + dexamethasone (40 mg weekly); dose escalation guided by mTPI-2: target toxicity probability = 0.25, EI = (0.2, 0.3); maximum dose sample size = 18 + 6 for BGB-11417 RP2D + carfilzomib 56 mg/m² + dexamethasone. [c]Can open as soon as the dose combination of BGB-11417 (RP2D-1) + carfilzomib (70 mg/m²) + dexamethasone is suggested to be eliminated and data of BGB-11417 (RP2D-1) + carfilzomib (56 mg/m²) + dexamethasone allow for further dose escalation per mTPI-2 decision table.

RESULTS

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	BGB-11417 (80 mg) (n=3)	BGB-11417 (160 mg) (n=3)	BGB-11417 (320 mg) (n=3)	BGB-11417 (640 mg) (n=3)	All patients (N=12)
Median age (range), years	62 (59-74)	70 (61-81)	68 (52-79)	74 (66-74)	69 (52-81)
Sex, n (%)					
Male	2 (67)	0	1 (33)	1 (33)	4 (33)
Female	1 (33)	3 (100)	2 (67)	2 (67)	8 (67)
ECOG PS, n (%)					
0	1 (33)	3 (100)	2 (67)	1 (33)	7 (58)
1	2 (67)	0	1 (33)	2 (67)	5 (42)
R-ISS stage at initial diagnosis, n (%)					
Stage I	0	2 (67)	0	1 (33)	3 (25)
Stage II	1 (33)	1 (33)	2 (67)	1 (33)	5 (42)
Stage III	2 (67)	0	1 (33)	0	3 (25)
Missing	0	0	0	1 (33)	1 (8)
Mean time from most recent R/R episode to first dose (SD), months	2 (1.5)	6 (5.4)	1 (0.5)	3 (2.2)	3 (3.2)
Cytogenic risk, n (%)					
High	0	1 (33)	0	1 (33)	2 (17)
Normal risk	1 (33)	1 (33)	2 (67)	2 (67)	6 (50)
Unknown	2 (67)	1 (33)	1 (33)	0	4 (33)
Number of prior lines, n (%)					
1	0	0	1 (33)	0	1 (8)
2-3	0	2 (67)	2 (67)	1 (33)	5 (42)
>3	3 (100)	1 (33)	0	2 (67)	6 (50)
Prior exposure					
anti-CD38 monoclonal antibodies	3 (100)	0	1 (33)	2 (67)	6 (50)

Data cutoff: 16 September 2022.

Table 2. Overall Safety Summary and DLT for BGB-11417 + Dexamethasone (40 mg weekly)

AEs, n (%)	BGB-11417 (80 mg) (n=3)	BGB-11417 (160 mg) (n=3)	BGB-11417 (320 mg) (n=3)	BGB-11417 (640 mg) (n=3)	All patients (N=12)
Patients with ≥1 treatment related AE	2 (67)	3 (100)	3 (100)	1 (33)	9 (75)
Grade ≥3 AEs	0	0	0	0	0
Serious	0	0	0	0	0
Leading to death	0	0	0	0	0
Leading to dose interruption					
Dose interruption of BGB-11417	0	0	0	0	0
Dose interruption of dexamethasone	0	0	0	0	0
Leading to dose reduction					
Dose reduction of BGB-11417	0	0	0	0	0
Dose reduction of dexamethasone	2 (67)	2 (67)	1 (33)	1 (33)	6 (50)
Leading to treatment discontinuation					
Discontinuation of BGB-11417	0	0	0	0	0
Discontinuation of dexamethasone	0	0	0	0	0
DLT	0	0	0	0	0

Data cutoff: 16 September 2022.

Table 3. Any Grade Treatment-Emergent AEs Occurring in ≥2 Patients

AEs, n (%)	BGB-11417 (80 mg) (n=3)	BGB-11417 (160 mg) (n=3)	BGB-11417 (320 mg) (n=3)	BGB-11417 (640 mg) (n=3)	All patients (N=12)
Insomnia	1 (33)	3 (100)	2 (67)	0	6 (50)
COVID-19	0	1 (33)	1 (33)	1 (33)	3 (25)
Fatigue	1 (33)	0	2 (67)	0	3 (25)
Alopecia	0	1 (33)	0	1 (33)	2 (17)
Arthralgia	1 (33)	0	1 (33)	0	2 (17)
Back pain	0	1 (33)	1 (33)	0	2 (17)
Dyspnea	0	0	2 (67)	0	2 (17)
Nausea	1 (33)	1 (33)	0	0	2 (17)

Data cutoff: 16 September 2022.

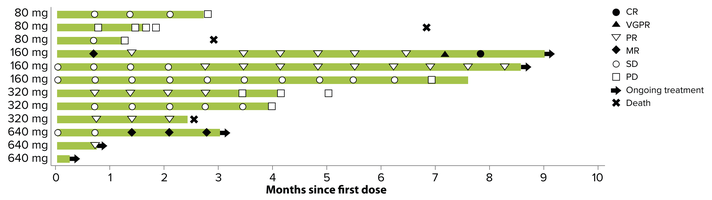
- One patient had grade 2 neutropenia, which did not lead to dose modifications or discontinuation

Table 4. Grade ≥3 Treatment-Emergent AEs

AEs, n (%)	BGB-11417 (80 mg) (n=3)	BGB-11417 (160 mg) (n=3)	BGB-11417 (320 mg) (n=3)	BGB-11417 (640 mg) (n=3)	All patients (N=12)
Alanine aminotransferase increased[a]	0	1 (33)	0	0	1 (8)
Aspartate aminotransferase increased[a]	0	1 (33)	0	0	1 (8)
Serum alkaline phosphatase increased[a]	0	1 (33)	0	0	1 (8)
Gamma-glutamyltransferase increased[a]	0	1 (33)	0	0	1 (8)
COVID-19	0	0	1 (33)	0	1 (8)

Data cutoff: 16 September 2022.
[a]Grade ≥3 treatment-emergent AEs included in this table were observed in the same patient.

Figure 2. Duration of Treatment and Best Response



Data cutoff: 16 September 2022.

Table 5. Disease Response by Investigator

AEs, n (%)	BGB-11417 (80 mg) (n=3)	BGB-11417 (160 mg) (n=3)	BGB-11417 (320 mg) (n=3)	BGB-11417 (640 mg) (n=3)	All patients (N=12)
Best overall response, n (%)					
sCR	0	0	0	0	0
CR	0	1 (33)	0	0	1 (8)
VGPR	0	0	0	0	0
PR	0	1 (33)	2 (67)	1 (33)	4 (33)
MR	0	0	0	1 (33)	1 (8)
SD	2 (67)	1 (33)	1 (33)	0	4 (33)
PD	1 (33)	0	0	0	1 (8)
Ongoing without post-baseline tumor assessment	0	0	0	1 (33)	1 (8)
ORR, n (%)	0	2 (68)	2 (67)	1 (33)	5 (42)
(95% CI)[a]	(0-71)	(9-99)	(9-99)	(1-91)	(15-72)
VGPR or BRR, n (%)	0	1 (33)	0	0	1 (8)
(95% CI)[a]	(0-71)	(1-91)	(0-71)	(0-71)	(0-39)

Data cutoff: 16 September 2022.
[a]The 95% CI was estimated using the Clopper-Pearson method.

CONCLUSIONS

- These early phase 1 results suggest that BGB-11417 is tolerable in combination with dexamethasone
  - No DLTs were seen across the 4 dose levels tested
  - No grade ≥3 TEAEs were observed
  - Toxicities were rare and manageable. The only hematologic toxicity seen was 1 case of grade 2 neutropenia, which did not lead to dose modifications or discontinuation
- BGB-11417 demonstrated activity at all tested dose levels, and most patients achieved disease control
  - One patient achieved CR in the 160 mg cohort
- Dose escalation is ongoing and RP2D was not achieved

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ABBREVIATIONS

AE, adverse event; Bcl-2, B-cell lymphoma 2; BRR, better response rate; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose limiting toxicity; ECOG, Eastern Cooperative Oncology Group; EI, equivalence interval; Ig, immunoglobulin; MCL1, myeloid leukemia cell differentiation protein; MAD, maximum assessed dose; MM, multiple myeloma; MR, minimal response; MTD, maximum tolerated dose; mTPI-2, modified toxicity probability interval; NE, non evaluable; ORR, overall response rate; PD, progressive disease; PK, pharmacokinetics; PR, partial response; PS, performance status; R-ISS, Revised International Staging System; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

DISCLOSURES

DK: honoraria from MMRF, Curio Science, Aptitude Health, SINTOMA, CURE, Plexus Communications; advisory committee member of Sanofi, Arcellx, BMS
HQ: research funding from Amgen, GSK, Karyopharm, BMS, Antengene, Abbvie, Sanofi; honoraria from Amgen, GSK, Karyopharm, BMS, Antengene, Janssen, CSL; advisory committee member of Amgen, GSK, Karyopharm, BMS, Antengene, Janssen, CSL, Sanofi
AS: consultancy from BMS, Janssen, Amgen, Haemalogix, Abbvie, Pfizer; research funding from Janssen, AbbVie; honoraria from BMS, Janssen, Amgen, Haemalogix, Abbvie, Pfizer
ML: consultancy from Janssen; honoraria from BMS; speakers bureau member of Janssen, AbbVie
RC: employment by and stock options from BeiGene; stock ownership from GSK, Pfizer, and SAGA diagnostics
CD, SP, VM, HC: employed by and equity ownership with BeiGene
BD: research funding from Janssen, Arcellx, BMS, Sanofi, Caregen,Cartesian, Fate; honoraria from Karyopharm, BMS, Janssen, Sanofi, GSK, Amgen, Takeda; speakers bureau member of Karyopharm, Sanofi, Janssen; advisory committee member of Pfizer, Abbvie, Genentech

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