Preliminary Safety and Efficacy of BGB-11417, a Potent and Selective B-Cell Lymphoma 2 (BCL2) Inhibitor, in Patients With Acute Myeloid Leukemia

Abstract P590

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INTRODUCTION

- BCL2, a key regulator of apoptosis, is aberrantly expressed in many hematologic malignancies
- Venetoclax-based treatments have improved outcomes in patients with AML who are unfit for induction chemotherapy; however, concerns regarding disease resistance and gastrointestinal/hematological toxicities remain[1]
- BGB-11417 is a potent and highly selective investigational BCL2 inhibitor
  - Demonstrated superior antitumor activity compared with venetoclax in preclinical studies[2]
  - Favorable pharmacokinetic profile and excellent bioavailability and selectivity for BCL2 (<1 nM)[2]
  - Tolerable safety profile at doses up to 640 mg in a phase 1 monotherapy study[3]
- The safety and efficacy of BGB-11417 plus azacitidine in patients with AML were evaluated in the ongoing BGB-11417-103 study

OBJECTIVES

Primary

- To evaluate safety and tolerability of BGB-11417 in combination with azacitidine, determine RP2D (parts 1 and 2) and efficacy (CR+CRh rate) based on European LeukemiaNet 2017 Response Criteria with assessment of hematologic improvement (part 3)[4,5]

Secondary

- To assess the PK of BGB-11417 in combination with azacitidine

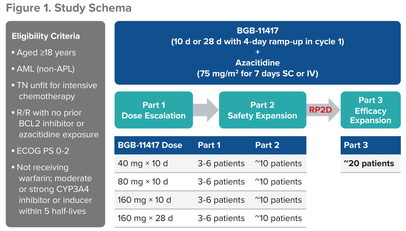
Exploratory

- To assess biomarker characteristics and correlation with efficacy

METHODS

- BGB-11417-103 is a phase 1b/2 dose-finding and expansion study of BGB-11417 (novel BCL2 inhibitor) in combination with azacitidine in patients with AML (**Figure 1**)

Figure 1. Study Schema



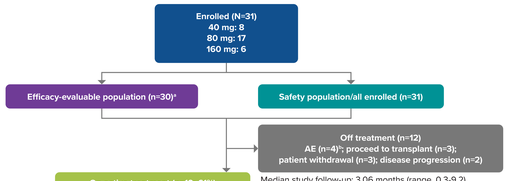
Safety Monitoring Committee reviews available patient safety and preliminary efficacy data to determine dose escalation in part 1, dose expansion to part 2, and the final RP2D to start part 3.

- Patients were to start allopurinol 2-3 days before first dose, with hospitalization during the ramp-up period in cycle 1 and regular laboratory monitoring
- DLTs were assessed in cycle 1 (**Figure 2**)
  - Patients with DLTs were assessed against the number of patients dosed, and the safety stopping criteria were based on the number of patients with events where posterior probability of event rate exceeding 0.25 was at least 80%
- Response assessments were performed every 3 cycles starting the end of cycle 1
- For patients not in remission, an additional response assessment was performed at the end of cycle 2
- MRD status was assessed by multiparameter flow cytometry at the end of cycle 1 and cycle 4

Figure 2. DLT Observation Window

RESULTS

Figure 3. Patient Disposition



Median study follow-up: 3.06 months (range, 0.3-9.2)
Median treatment duration: 2.40 months (range, 0.3-9.2)
Data cutoff: 28 February 2022

[a]The efficacy evaluable set included patients who completed at least 1 cycle of treatment (initiated the second cycle) or 42 days, whichever is earlier, or discontinued treatment during the first cycle.
[b]AE leading to treatment discontinuations: infections (bacterial sepsis, pulmonary sepsis, bronchopulmonary aspergillosis), anemia, and thrombocytopenia.

Table 1. Baseline Characteristics

Characteristics	TN (n=19)	R/R (n=12)	All (N=31)
Age, median (range), y	80 (64-87)	69 (36-78)	74 (36-87)
Female sex, n (%)	11 (57.9)	7 (58.3)	18 (58.1)
ECOG PS 0-1, n (%)	16 (84.2)	12 (100)	28 (90.3)
AML type, n (%)			
De novo	18 (94.7)	10 (83.3)	28 (90.3)
Secondary	1 (5.3)	2 (16.7)	3 (9.7)
AML risk stratifications, n (%)			
Favorable	3 (15.8)	1 (8.3)	4 (12.9)
Intermediate	7 (36.8)	5 (41.7)	12 (38.7)
Adverse	8 (42.1)	6 (50.0)	14 (45.2)

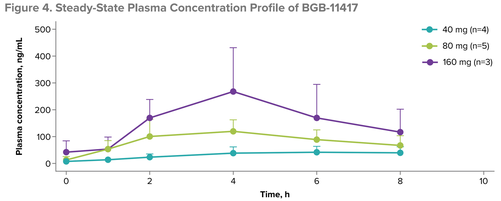
Table 2. Treatment Exposure in AML Cohorts

Treatment exposure, median (min, max)	40 mg × 10 d (n=8)		80 mg × 10 d (n=17)		160 mg × 10 d (n=6)		Total (N=31)	
	BGB-11417	Azacitidine	BGB-11417	Azacitidine	BGB-11417	Azacitidine	BGB-11417	Azacitidine
Duration of exposure, mo	1.31 (0.3, 4.8)	1.31 (0.2, 4.8)	2.96 (0.3, 9.2)	2.96 (0.2, 9.2)	1.95 (0.3, 3.7)	1.99 (0.2, 3.5)	2.40 (0.3, 9.2)	2.33 (0.2, 9.2)
Cycle duration, d	27.8 (8.0, 43.3)		30.0 (8.0, 40.6)		34.5 (25.7, 40.0)		30.0 (8.0, 43.3)	
Number of cycles, n	1.5 (1.0, 5.0)		3.0 (1.0, 9.0)		2.5 (1.0, 4.0)		3.0 (1.0, 9.0)	

Pharmacokinetics

- Preliminary steady state PK data from patients with AML who received the 40- to 160-mg target doses in combination with azacitidine
  - Steady state exposure (C_{max} and AUC_{0-8}) of BGB-11417 in combination azacitidine were comparable to that of BGB-11417 as monotherapy
  - Steady state C_{max} and AUC_{0-8} appeared to increase in a dose-dependent manner (**Figure 4**)
  - Steady state PK parameters were derived by noncompartmental analysis method using nominal sampling time and are summarized in **Table 3**

Figure 4. Steady-State Plasma Concentration Profile of BGB-11417



Error bars indicate ± standard deviation.

Table 3. Steady-State PK Parameters

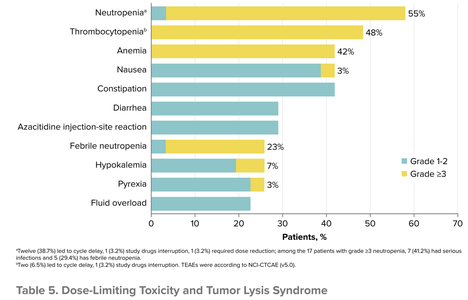
PK parameters	40 mg (n=4)	80 mg (n=5)	160 mg (n=3)
T_{max}, median (range), h	4 (4-6)	4 (2-4)	4 (2-4)
C_{max}, arithmetic mean (SD), ng/mL	62 (63.9)	130 (39.2)	249 (70.4)
AUC_{0-8}, arithmetic mean (SD), ng·hr/mL	350 (64.1)	692 (46.3)	1214.6 (66.1)

Table 4. Summary of TEAEs

TEAEs, n (%)	Total (N=31)
Any TEAE	31 (100.0)
Grade ≥3	27 (87.1)
Serious	22 (71.0)
Leading to treatment discontinuation	
BGB-11417	4 (12.9)[a]
Azacitidine	5 (16.1)[a,b]
Leading to death	3 (9.7)[c]
Leading to BGB-11417 reduction	1 (3.2)[d]
Leading to azacitidine reduction	1 (3.2)[d]

[a]TEAEs leading to discontinuation of both study drugs: fatal infections (n=3; bacterial sepsis, bronchopulmonary aspergillosis, pulmonary sepsis); anemia and thrombocytopenia (n=1).
[b]TEAE leading to discontinuation of azacitidine: injection site reaction (n=1).
[c]Fatal infections in the setting of AML-related neutropenia (n=2) and disease progression (n=1); all were considered unrelated to study treatment.
[d]TEAE leading to BGB-11417 dose reduction: neutropenia (n=1).
[e]TEAE leading to azacitidine dose reduction: neutrophil count decreased (n=1).

Figure 5. Most Common TEAEs (≥20% for All Grades)



[a]Twelve (38.7%) led to cycle delay, 1 (3.2%) study drugs interruption, 1 (3.2%) required dose reduction; among the 17 patients with grade ≥3 neutropenia, 7 (41.2%) had serious infections and 5 (29.4%) has febrile neutropenia.
[b]Two (6.5%) led to cycle delay, 1 (3.2%) study drugs interruption. TEAEs were according to NCI-CTCAE (v5.0).

Table 5. Dose-Limiting Toxicity and Tumor Lysis Syndrome

	BGB-11417			
	40 mg × 10 d (n=5)	80 mg × 10 d (n=15)	160 mg × 10 d (n=6)	Total[b] (N=26)
DLT,[a] n (%)	0	2 (13.3)	0	2 (7.7)
Hematologic	0	2 (13.3)	0	3 (11.5)
Grade 4 neutropenia	0	1 (6.7)	0	1 (3.8)
Grade 4 thrombocytopenia	0	2 (13.3)	0	2 (7.7)
Nonhematologic (grade ≥3)	0	0	0	0
Hy's Law	0	0	0	0
Laboratory TLS,[c] n (%)	0	0	1 (16.7)[d]	1 (3.2)

[a]DLT was assessed through cycle 1 day 28 (nonhematologic) and up to day 42 or initiation of cycle 2 (hematologic).
[b]Based on DLT evaluable set, which includes patients who completed the DLT observation window and received ≥80% of the intended cumulative dose.
[c]TLS assessment based on the Howard criteria.[6]
[d]Occurred on day 4 of cycle 2 in an 85-year-old patient with known chronic kidney disease; he was asymptomatic and recovered after 4 days.

- CR/CRh achieved in 58% TN and 55% R/R patients, with most CRs achieved by the end of cycle 1: 11 of 17 CR/CRh and 7 of 11 CRs (**Table 6**, **Figure 6**)
- Thirteen patients met CR/CRi with evaluable flow cytometry MRD results, 5 (38.5%) of the 13 achieved MRD negativity (malignant AML <0.1% per ELN 2018),[7] and 2 of 5 were MRD negative after 1 cycle of treatment (**Table 6**)
- Most patients had ≥80% reduction in bone marrow blast (**Figure 7**)

Table 6. Best Overall Response

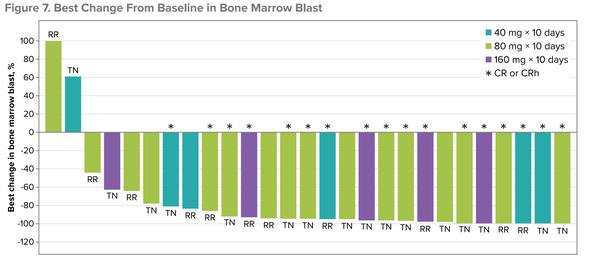
	40 mg × 10 d		80 mg × 10 d		160 mg × 10 d		Total	
	TN (n=4)	R/R (n=3)	TN (n=11)	R/R (n=6)	TN (n=4)	R/R (n=2)	TN (n=19)	R/R (n=11)
CR+CRh, n (%)	2 (50)	2 (67)	7 (64)	2 (33)	2 (50)	2 (100)	11 (58)	6 (55)
CR+CRh after 1 cycle	2 (50)	1 (33)	5 (45)	1 (17)	2 (50)	0	9 (47)	2 (18)
CR+CRi, n (%)	2 (50)	2 (67)	7 (64)	3 (50)	2 (50)	2 (100)	11 (58)	7 (64)
MRD evaluable[a]	2	1	6	2	1	1	9	4
MRD negative	1	0	3	1	0	0	4	1
CR	2 (50)	0	6 (55)	1 (17)	1 (25)	1 (50)	9 (47)	2 (18)
CRi	0	2 (67)	1 (9)	2 (33)	1 (25)	1 (50)	2 (11)	5 (46)
ORR (CR+CRi+MLFS+PR), n (%)	2 (50)	2 (67)	10 (91)	3 (50)	2 (50)	2 (100)	14 (74)	7 (64)
MLFS	0	0	2 (18)	0	0	0	2 (11)	0
PR	0	0	1 (9)	0	0	0	1 (5)	0
Time to CR, median, mo	1.31	N/A	1.36	3.75	0.95	1.94	1.31	2.84
Response assessment not done, n (%)	1 (25)	0	1 (9)	0	1 (25)	0	3 (16)	0
BGB-11417 treatment duration, median (range), mo	1.31 (0.3-4.8)		2.96 (0.3-9.2)		1.95 (0.3-3.7)		2.40 (0.3-9.2)	

[a]MRD status was determined from the percentage of malignant AML cells in CD45+ cells in the bone marrow as measured by multiparameter flow cytometry (using leukemia-associated immunophenotype-based Different from Normal approach). Lower limit of detection <0.1% in evaluable samples was used as the cut-off per ELN 2018. Flow cytometry MRD results were not available in some patients with CR/CRi due to sample quality issue or pending sample analysis.

Figure 6. Best Overall Response Over Time

The efficacy evaluable set included patients who completed at least 1 cycle of treatment (initiated the second cycle) or 42 days, whichever is earlier, or discontinued treatment during the first cycle. Response assessments were not done in 3 TN patients in each dose group and are not shown in the graph.

Figure 7. Best Change From Baseline in Bone Marrow Blast



CONCLUSIONS

- Preliminary results showed that the 10-day regimen of BGB-11417 (40, 80, 160 mg) plus azacitidine was well tolerated and active in patients with AML across the 3 dose levels tested
  - 58% TN and 55% R/R patients with AML met CR+CRh criteria
    - Most CRs (7 of 11) were achieved by the end of cycle 1
    - Five of 13 (38.5%) evaluable CR/CRi achieved MRD negativity
  - Neutropenia (54.8%) was the most common grade ≥3 AE
    - Manageable with growth factor support and dose modification
  - DLTs (grade 4 neutropenia/thrombocytopenia) occurred in 2 patients (safety stopping criteria were not met)
  - Four patients discontinued study treatment due to AEs
    - Three died from unrelated infections (sepsis and aspergillosis)
    - One due to treatment-related anemia and thrombocytopenia
- Enrollment in the safety expansion is ongoing; evaluation of 28-day dosing regimen is planned

ABBREVIATIONS

AE, adverse event; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; AUC, area under the curve; BCL2, B-cell lymphoma 2; BOR, best overall response; C1, end of cycle 1 or day 42; C2, end of cycle 2; C_{max}, maximum concentration; CR, complete remission; CRi, CR with incomplete hematologic recovery; CRh, CR with partial hematologic recovery; CYP3A4, cytochrome P450 3A4; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; LAIP, leukemia-associated immunophenotype; MLFS, morphologic leukemia-free state; PK, pharmacokinetics; PD, progressive disease; PR, partial remission; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; SD, stable disease; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; T_{max}, time to maximum concentration; TN, treatment naive.

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DISCLOSURES

JS: consulting role with Astellas, Mundipharma, Novartis; research funding from Astex, Amgen, BMS/Celgene
CYF: honoraria from AbbVie, Astellas, Amgen, BMS, Novartis, Pfizer; consulting role with AbbVie, Astellas, Amgen, BMS, Novartis, Pfizer; research funding from Astellas; speakers bureau for AbbVie, Amgen, Pfizer
RR: stock ownership with CSL Behring; honoraria with AbbVie; consulting role with Janssen
RG: honoraria from AbbVie, MSD, Astellas, Janssen, Antengene
CG: advisory board participation for AbbVie and Astellas
DL: employment with Central West Haematology; speakers bureau for Janssen
PT: research funding from Novartis, Celgene, Janssen, and Epimab
CD: honoraria from AbbVie, Agios, Celgene, Servier, BMS, Celgene, Novartis, Takeda, Jazz; consulting role with BMS, Celgene, Servier, Kura, GSK, Genmab; research funding from AbbVie, Agios, Servier, BMS, Foghorn, Immune-Onc, Lilly
MTL: employment and stock ownership with BeiGene; patents from Davos Life Science Pte Ltd
SC, YL, MC, DS: employment and stock ownership with BeiGene
WYC: employment with BeiGene; stock ownership with BeiGene, BMS
AHW: consulting role with AbbVie, Servier, Pfizer, Roche, Novartis, Astellas, Janssen, Amgen, Gilead, BMS, MacroGenics, Agios; research funding from Novartis, AbbVie, Servier, BMS, Syndax, Atea, AstraZeneca, Amgen; speakers bureau for AbbVie, Novartis, BMS, Astellas; intellectual property interests with the Walter and Eliza Hall Institute of Medical Research
PC, TFN, SR, SL, SYT: nothing to disclose

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