Preliminary Safety and Efficacy of BGB-11417, a Novel Bcl-2 Inhibitor, in Combination With Azacitidine in Patients With Acute Myeloid Leukemia

Jake Shortt,[1] Pau Montesinos,[2] Shuh Ying Tan,[3] Teng Fong Ng,[4] Chun Yew Fong,[5] Paul Cannell,[6] Sophie Leitch,[7] Peter Tan,[8] Sundra Ramanathan,[9] Robin Gasiorowski,[10] Douglas Lenton,[11] Tse-Chieh Teh,[12] José Antonio Pérez-Simón,[13] Carolyn Grove,[14] Xiaojun Huang,[15] Courtney DiNardo,[16] Katherine Naidu,[17] Si Cheng,[17] Yu Liu,[17] Melannie Co,[17] Wai Y. Chan,[17] Haiyi Guo,[17] and Andrew H. Wei[18]

[1]Monash Health and Monash University, Clayton, Victoria, Australia; [2]Hospital Politecnico Universitario La Fe, Valencia, Spain; [3]St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia; [4]Gold Coast University Hospital, Southport, Queensland, Australia; [5]Austin Health, Heidelberg, Victoria, Australia; [6]Fiona Stanley Hospital, Murdoch, Western Australia, Australia; [7]North Shore Hospital, Auckland, New Zealand; [8]One Clinical Research, Nedlands, Western Australia, Australia; [9]The Saint George Hospital-Kogarah, Kogarah, New South Wales, Australia; [10]Concord Repatriation General Hospital, Concord West, New South Wales, Australia; [11]Orange Health Service (Central West Cancer Care Centre), Orange, New South Wales, Australia; [12]Department of Clinical Haematology, The Alfred Hospital, Prahran, Victoria, Australia; [13]Hospital Universitario Virgen del Rocio, Instituto de Biomedicina de Sevilla (IBS/CISC), Universidad de Sevilla, Spain; [14]Linear Clinical Research, PathWest & Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia; [15]Peking University People's Hospital, Beijing, China; [16]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [17]BeiGene (Shanghai) Co., Ltd., Shanghai, China and BeiGene USA, Inc., San Mateo, CA, USA; and [18]Department of Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Victoria, Australia

INTRODUCTION

- The efficacy of Bcl-2 inhibitors in combination with hypomethylating agents for treating newly diagnosed AML ineligible for intensive chemotherapy has been confirmed by phase 3 studies[1]
  - However, AML survival rates beyond 2 years are low[1]
- BGB-11417 is a potent and selective Bcl-2 inhibitor with the potential to achieve deeper target inhibition and responses in the clinical setting[2]
  - In an AML xenograft model (human MOLM-13), BGB-11417 demonstrated a greater anti-tumor reduction than venetoclax at the same dose level, alone and when combined with azacitidine[3]
  - Tolerable safety profile up to 640 mg as evaluated in a phase 1 dose-escalation study[4]
  - Preliminary pharmacokinetic results showed dose-dependent increase in exposures[5]
- Here, we present updated preliminary results of patients with AML enrolled in BGB-11417-103 (NCT04771130)

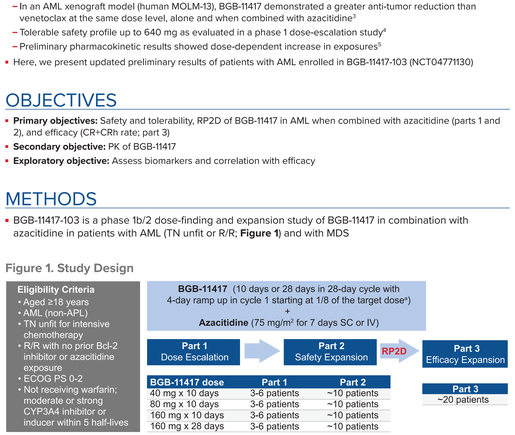
OBJECTIVES

- **Primary objectives:** Safety and tolerability, RP2D of BGB-11417 in AML when combined with azacitidine (parts 1 and 2), and efficacy (CR+CRh rate; part 3)
- **Secondary objective:** PK of BGB-11417
- **Exploratory objective:** Assess biomarkers and correlation with efficacy

METHODS

- BGB-11417-103 is a phase 1b/2 dose-finding and expansion study of BGB-11417 in combination with azacitidine in patients with AML (TN unfit or R/R; **Figure 1**) and with MDS

Figure 1. Study Design



[a]Patients were hospitalized during the ramp-up period for TLS monitoring.[1]
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.

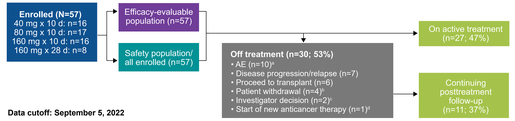
- DLTs were assessed in cycle 1 (**Figure 2**)
  - Patients were DLT evaluable if they received ≥80% the intended cumulative dose in cycle 1
- Response assessments based on European LeukemiaNet 2017 Response Criteria with assessment of hematologic improvement[7,8] were performed every 3 cycles starting at 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[9] at the end of cycles 1 and 4, and at the end of cycle 2 if additional response assessment was performed

Figure 2. DLT Observation Window

RESULTS

- As of the data cutoff of 5 September 2022, 57 patients with AML were enrolled and dosed (31 TN unfit and 26 R/R) in 4 dose cohorts (**Figure 3**)
- The median follow-up time was 5.3 months (range, 0.2-15.4) and the median treatment duration was 3.0 months (range, 0-15.4)

Figure 3. Patient Disposition



Data cutoff: September 5, 2022

[a]AE leading to discontinuation of both study drugs: bacterial sepsis, pulmonary sepsis, neutropenic sepsis, bronchopulmonary aspergillosis, pneumonia, sepsis, septic shock, anemia, thrombocytopenia, metastatic squamous cell carcinoma, aortobronchial fistula. [b]Patient withdrawal: unable to adhere to study visits (n=2), requested no further treatment of AML/palliative care (n=2). [c]Investigator decision: no appreciable response after 2 cycles, switched to chemotherapy (n=1), patient was nonadherent (n=1). [d]Without disease progression.

Table 1. Baseline Characteristics

Characteristics, n (%)	TN (n=31)	R/R (n=26)	All (N=57)
Median age (range), years	77 (64-91)	64 (29-80)	71 (29-91)
Male	19 (61)	16 (62)	35 (61)
AML type			
De novo	26 (84)	23 (88)	49 (86)
AML risk stratifications[a]			
Intermediate	11 (35)	8 (31)	19 (33)
Adverse	11 (35)	13 (50)	24 (42)
Bone marrow blast count			
≥30 to <50%	11 (35)	3 (12)	14 (25)
≥50%	12 (39)	11 (42)	23 (40)
Most common genetic abnormalities			
inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*	3 (10)	7 (27)	10 (18)
NPM1	4 (13)	5 (19)	9 (16)
-7 or del(7q)	5 (16)	3 (12)	8 (14)
Complex karyotype or monosomal karyotype	5 (16)	3 (12)	8 (14)
-5 or del(5q)	5 (16)	2 (8)	7 (12)
IDH1	2 (6)	5 (19)	7 (12)
RUNX1	2 (6)	4 (15)	6 (11)
FLT3[b]	4 (13)	2 (8)	6 (11)
IDH2[c]	1 (3)	5 (19)	6 (11)
TP53 aneuploidy	4 (13)	1 (4)	5 (9)
t(8;21)(q22;q22.1); *RUNX1-RUNX1T1*	3 (10)	1 (4)	4 (7)

[a]Based on ELN 2017 risk stratifications by genetics. [b]FLT3-ITD (low or high allelic ratio), none FLT3-TKD. [c]Includes R140 and R172 mutations.

- Most patients had 3 cycles of treatment. Patients in the 80 mg x 10 days cohort had the longest duration of treatment (median of 7 cycles, **Table 2**)

Table 2. Treatment Exposure in AML

	40 mg x 10 d (n=16)		80 mg x 10 d (n=17)		160 mg x 10 d (n=16)		160 mg x 28 d (n=8)		Total (N=57)	
	BGB-11417	Aza	BGB-11417	Aza	BGB-11417	Aza	BGB-11417	Aza	BGB-11417	Aza
Median duration of treatment (min, max), mo	3.3 (0.3, 10.6)	3.3 (0.2, 10.6)	7.8 (0.3, 15.4)	7.8 (0.2, 15.4)	3.1 (0.1, 9.9)	3.1 (0.1, 9.7)	2.2 (0, 4.1)	1.6 (0.1, 3.7)	3.0 (0, 15.4)	3.0 (0.1, 15.4)
Median cycle duration[a] (min, max), d	32 (13, 44.5)		33 (8, 40.6)		34 (5, 40.0)		38 (2, 51.7)		33 (2, 51.7)	
Median no. of cycles (min, max)	3(1, 11)		7 (1, 14)		3 (1, 10)		2 (1, 4)		3(1, 14)	

[a]Each cycle duration should be 28 days. If initiation of the following cycle is delayed for any reason, the cycle duration will be measured up to the last day before the next cycle was initiated or treatment discontinuation, whichever occurred first.

SAFETY

- Six patients had a TEAE leading to death, by infection (n=5; 4 TN, 1 R/R) and aortobronchial fistula (n=1 R/R; **Table 3**)
  - Pulmonary sepsis (40 mg x 10 d; in a patient with COPD); hospital-acquired pneumonia (80 mg x 10 d; in a patient with baseline neutropenia); bronchopulmonary aspergillosis (80 mg x 10 d; occurred following disease progression), neutropenic sepsis (160 mg x 10 d; in a patient with type II diabetes, related to underlying AML); sepsis (160 mg x 10 d; occurred following disease progression), and aortobronchial fistula (160 mg x 28 d; complication of a thoracic aneurysm)

Table 3. Summary of TEAEs

TEAEs, n (%)	Total (N=57)
Any TEAE	57 (100)
Grade ≥3	53 (93)
Serious	46 (81)
Leading to death	6 (11)
Death within 30 days of first dose	1 (2)
Death within 60 days of first dose	3 (5)
Leading to discontinuation	
BGB-11417	10 (18)
Azacitidine	11 (19)
Leading to reduction	
BGB-11417	6 (11)
Azacitidine	9 (16)
Leading to cycle delays	
BGB-11417	37 (65)
Azacitidine	37 (65)

- Neutropenia, thrombocytopenia and febrile neutropenia were the most common reasons for cycle delays. The median cycle duration was 33 days (**Table 2**)
  - DLT (grade 4 neutropenia and thrombocytopenia lasting beyond day 42) occurred in 2 patients in the 80 mg x 10 days cohort. No new DLTs were observed with higher doses (**Table 4**)
  - No clinical TLS was observed. Laboratory TLS occurred in a patient treated with 160 mg x 10 days (assessed based on Howard criteria[9]). This patient had pre-existing history of chronic kidney disease. He was managed successfully as an outpatient and fully recovered after 4 days

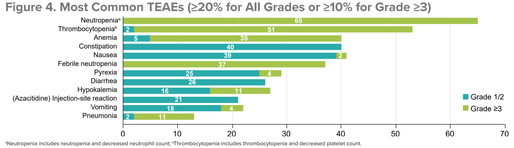
Table 4. DLTs and TLS

	BGB-11417				
DLT evaluable[a], n (%)	40 mg x 10 d (n=14)	80 mg x 10 d (n=15)	160 mg x 10 d (n=15)	160 mg x 28 d (n=6)	Total (n=50)
DLT	0	2 (13)	0	0	2 (4)
Hematologic	0	2 (13)	0	0	2 (4)
Grade 4 neutropenia	0	1 (7)	0	0	1 (2)
Grade 4 thrombocytopenia	0	2 (13)	0	0	2 (4)
Nonhematologic (grade ≥3)	0	0	0	0	0

[a]Based on DLT evaluable set, which includes patients who completed the DLT observation window and received ≥80% of the intended cumulative dose.

- The most common TEAEs were neutropenia, thrombocytopenia and anemia, and the most common non-hematologic TEAEs were nausea and constipation (majority were grade 1/2, **Figure 4**)

Figure 4. Most Common TEAEs (≥20% for All Grades or ≥10% for Grade ≥3)



[a]Neutropenia includes neutropenia and decreased neutrophil count; [b]Thrombocytopenia includes thrombocytopenia and decreased platelet count.

EFFICACY

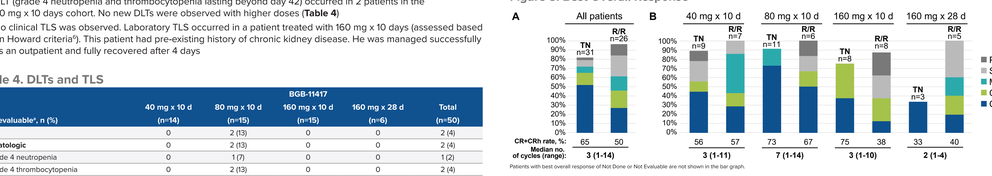
- CR+CRh was achieved in 65% of TN and 50% of R/R patients (**Table 5**)
  - Most CR+CRh in TN AML (15 of 20) was achieved by the end of cycle 1
- The 80 mg x 10 day cohort (n=17) had the longest treatment duration with a median of 7 cycles (**Figure 5**)
  - CR+CRh was seen in 73% and 67% of TN and R/R patients, respectively
  - CR was seen in 73% and 50% of TN and R/R patients, respectively
- Reduction in bone marrow blast is shown in **Figure 6**
- Twenty-seven patients met CR+CRh with evaluable flow cytometry MRD results, and 13 (48%) of the 27 achieved MRD negativity (malignant AML <0.1% per ELN 2018[9])

Table 5. Summary of Complete Responses

Response	40 mg x 10 d		80 mg x 10 d		160 mg x 10 d		160 mg x 28 d		Total	
	TN (n=9)	R/R (n=7)	TN (n=11)	R/R (n=6)	TN (n=8)	R/R (n=8)	TN (n=3)	R/R (n=5)	TN (n=31)	R/R (n=26)
CR+CRh, n (%)	5 (56)	4 (57)	8 (73)	4 (67)	6 (75)	3 (38)	1 (33)	2 (40)	20 (65)	13 (50)
CR+CRh after 1 cycle	4 (44)	1 (14)	5 (45)	1 (17)	5 (63)	1 (13)	1 (33)	2 (40)	15 (48)	5 (19)
CR+CRi, n (%)	5 (56)	3 (43)	8 (73)	4 (67)	6 (75)	3 (38)	1 (33)	2 (40)	20 (65)	12 (46)
CR	4 (44)	2 (29)	8 (73)	3 (50)	3 (38)	1 (13)	1 (33)	1 (20)	16 (52)	7 (27)
Median time to CR, mo	1.3	3.2	1.8	3.8	1.2	1.9	1.2	1.1	1.3	3.8
Median BGB-11417 treatment duration (range), mo	4.9 (0.3-10.6)	1.7 (1.3-6.2)	7.8 (0.3-15.2)	7.3 (0.4-15.4)	3.3 (0.3-9.9)	2.3 (0.1-9.7)	1.4 (0.0-2.7)	2.3 (0.9-4.1)	3.7 (0.0-15.2)	2.6 (0.1-15.4)

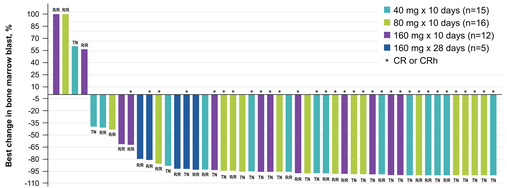
[a]CRh was defined by Bloomfield et al.[7]
Response assessments based on 2017 ELN response criteria with assessment of hematologic improvement (part 3).[10]
Number of patients who did not have a posttreatment response assessment: in TN 40 mg and 80 mg (n=1 each), in TN 160 mg x 10 days and x 28 days (n=2 each), and in R/R 160mg x 10 days (n=1).

Figure 5. Best Overall Response



Patients with best overall response of Not Done or Not Evaluable are not shown in the bar graph.

Figure 6. Best Change From Baseline in Bone Marrow Blasts



CONCLUSIONS

- BGB-11417 (40, 80, 160 mg) plus azacitidine was generally well tolerated in patients with AML
  - DLTs (grade 4 neutropenia/thrombocytopenia) only occurred in the 80 mg cohort; no new DLTs occurred with further dose escalation
  - Neutropenia (65%) was the most common grade ≥3 TEAE, manageable with dose modifications and supportive care
  - No dose-dependent toxicities were observed
  - Maximum tolerated dose was not reached
- The combination was effective in both TN and R/R settings at the four dose levels tested
  - CR/CRh was achieved in 65% TN and 50% R/R patients
- Efficacy analysis of molecular subgroups, safety expansion, and evaluation of higher doses of BGB-11417 are ongoing; inclusion of patients with AML who failed hypomethylating agents is also planned

REFERENCES

1. DiNardo et al. *N Engl J Med* 2020;383(7):617-629
2. Hu et al. *Cancer Res* 2020;80(suppl 16):3077
3. Data on file. BGB-11417 Investigator Brochure
4. Opat et al. EHA 2022. Abstract P687
5. Shortt et al. EHA 2022. Abstract P590
6. Howard SC, et al. *N Engl J Med* 2011;364(19):1844-1854. Erratum in *N Engl J Med* 2018;379(11):1094
7. Bloomfield CD, et al. *Blood Rev* 2018;32(5):416-425
8. Döhner H, et al. *Blood* 2017;129(4):424-447
9. Schuurhuis GJ, et al. *Blood* 2018;131(12):1275-1291

ABBREVIATIONS

AE, adverse event; AML, acute myeloid leukemia; aza, azacitidine; BCL2, B-cell lymphoma 2; COPD, chronic obstructive pulmonary disease; CR, complete response; CRh, complete response with partial hematologic recovery; CYP3A4, cytochrome P450 3A4; D, day; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; ITD, internal tandem duplication; IV, intravenous; MLFS, morphological leukemia-free state; MDS, myelodysplastic syndrome; MRD, minimal residual disease; PD, progressive disease; PI, principal investigator; PK, pharmacokinetics; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SC, subcutaneous; SD, stable disease; TEAE, treatment-emergent adverse event; TKD, tyrosine kinase domain; TLS, tumor lysis syndrome; TN, treatment naive.

DISCLOSURES

JS: consulting for Otsuka, Astellas, Novartis, Mundipharma, BMS; research funding from Amgen, Astellas, BioCurate; speakers bureau for Mundipharma
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KM: honoraria from AbbVie
RG: honoraria from AbbVie, Astellas, Janssen, MSD, Novartis, Otsuka, Takeda
PT: research funding from Novartis, Celgene, Janssen, and Epimab
JAPS: consulting and advisory role for Novartis, Jansen, Gilead, Jazz, Takeda, Alexion; research funding from Takeda, AbbVie, Pfizer; honoraria and travel expenses from Novartis, Jansen, Gilead, Jazz, Takeda, Alexion
CG: advisory board for AbbVie, Astellas, Otsuka
XH: consulting for Astellas, Takeda, Janssen, Pfizer, MSD, Sanofi, BeiGene; research funding from BeiGene, Sanofi, Astellas; honoraria from Astellas, Takeda, Janssen, Pfizer, MSD, Sanofi, BeiGene; travel expenses from BeiGene
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KN, JP, SC, YL, MC, HG: employment and stock ownership with BeiGene
WYC: employment and stock with BeiGene; stock with BMS
AHW: consulting for Servier, BeiGene, AbbVie, Novartis; research funding from Novartis, AbbVie, Servier, Janssen, BMS, Syndax, Astex, AstraZeneca, Amgen; honoraria from Novartis, AstraZeneca, Astellas, Janssen, Amgen, Roche, Pfizer, AbbVie, Servier, Gilead, BMS, Shoreline, MacroGenics, Agios; speakers bureau for AbbVie, Novartis, Servier, BMS, Astellas; travel expenses from Novartis, Servier; patent with Servier
SYT, PC, SL, SR, DL, TCT: nothing to disclose

CORRESPONDENCE

Jake Shortt, MD, PhD
Monash Health and Monash University
Clayton, Victoria, Australia
jake.shortt@monashhealth.org

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