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

Authors: Jake Shortt,[1] Pau Montesinos,[2] Shuh Ying Tan,[3] Teng Fong Ng,[4] Chun Yew Fong,[5] Paul Cannell,[6] Rajeev Rajagopal,[7] Sophie Leitch,[8] Peter Tan,[9] Sundra Ramanathan,[10] Robin Gasiorowski,[11] Douglas Lenton,[12] Tse-Chieh Teh,[13] José Antonio Pérez-Simón,[14] Carolyn Grove,[15] Xiaojun Huang,[16] Courtney DiNardo,[17] Katherine Naidu,[18] Joseph Pariseau,[18] Si Cheng,[18] Yu Liu,[18] Melannie Co,[18] Wai Y. Chan,[18] Haiyi Guo,[18] and Andrew H. Wei[19]

Affiliations: *[1]School of Clinical Sciences, Monash University and Monash Health, 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]Middlemore Hospital, Auckland, New Zealand; [8]North Shore Hospital, Auckland, New Zealand; [9]One Clinical Research, Nedlands, Western Australia, Australia; [10]The Saint George Hospital-Kogarah, Kogarah, New South Wales, Australia; [11]Concord Repatriation General Hospital, Concord West, New South Wales, Australia; [12]Orange Health Service (Central West Cancer Care Centre), Orange, New South Wales, Australia; [13]Department of Clinical Haematology, The Alfred Hospital, Prahran, Victoria, Australia; [14]Hospital Universitario Virgen del Rocio, Instituto de Biomedicina de Sevilla (IBIS / CISC), Universidad de Sevilla, Spain; [15]Linear Clinical Research, PathWest & Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia; [16]Peking University People's Hospital, Beijing, China; [17]University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [18]BeiGene (Shanghai) Co., Ltd., Shanghai, China and BeiGene USA, Inc., San Mateo, CA, USA; and [19]Department of Clinical Haematology, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, Victoria, Australia*

Background/Introduction: The efficacy of Bcl-2 inhibitors for treating AML was recognized by the approval of venetoclax and azacitidine (aza) in patients (pts) with newly diagnosed AML ineligible for intensive chemotherapy. However, survival rates beyond 2 years are low. Compared to venetoclax, BGB-11417 is a much more potent Bcl-2 inhibitor (>10-fold in biochemical assays) with improved selectivity and the potential to achieve deeper target inhibition and responses in the clinical setting. Here, we present updated preliminary results of pts with AML enrolled in BGB-11417-103 (NCT04771130).

Methods: BGB-11417-103 is an ongoing dose finding/expansion study evaluating BGB-11417 and aza in pts with AML (treatment-naïve [TN] unfit for intensive chemotherapy or relapsed/refractory [R/R]), myelodysplastic syndrome (MDS), or MDS/myeloproliferative neoplasm. For all indications, pts who received prior aza or Bcl-2 inhibitors were excluded. For pts with AML, the 10-day regimen comprised BGB-11417 at 40 mg (cohort 1), 80 mg (cohort 2), or 160 mg (cohort 3); 160 mg was also used in a 28-day regimen (cohort 4). All dose levels were given in combination with aza (75 mg/m^2 x 7 days). In cycle 1, a 4-day ramp-up of BGB-11417 starting at 1/8 target dose was used. Patients with dose-limiting toxicities (DLTs) in cycle 1 were assessed against the number of patients dosed. 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%. Responses were determined using 2017 European LeukemiaNet (ELN) criteria with assessment of hematologic improvement. Treatment-emergent adverse events (TEAEs), minimal residual disease (MRD) by flow cytometry, and pharmacokinetics (PK) were also assessed.

Results: As of June 1, 2022, 51 pts with AML were treated (16 in cohort 1; 17 in cohort 2; 14 in cohort 3; 4 in cohort 4). Median age was 77 yrs (TN, n=28) and 64 yrs (R/R, n=23) (**Table 1**). At baseline, 23 pts

(45.1%) had adverse-risk cytogenetics, 37 (72.5%) had grade ≥3 neutropenia, and 27 (52.9%) had grade ≥3 thrombocytopenia.

At a median follow-up of 2.8 mo (range 0.1-12.3) and median duration of treatment of 1.9 mo (range 0.0-12.3), 2 of 41 evaluable pts experienced DLTs (grade 4 neutropenia and grade 4 thrombocytopenia at 80 mg) (**Table 2**), which did not meet the safety stopping protocol criteria. Laboratory tumor lysis syndrome (TLS; Howard criteria) was observed in 1 pt (160 mg x 10 days) with a known history of chronic kidney disease; TLS resolved within 4 days.

Twenty-one (41%) pts discontinued study drugs: 7 (13.7%) due to AEs, 5 (9.8%) due to disease progression, 4 (7.8%) proceeded to transplant, 3 (5.9%) withdrew consent, 1 (2.0%) per investigator decision, and 1 (2.0%) started new anti-cancer treatment.

The most common TEAEs were neutropenia (58.8%), thrombocytopenia (45.1%), anemia (43.1%), febrile neutropenia (33.3%), nausea (39.2%), and constipation (37.3%). Neutropenia was the most common grade ≥3 TEAE observed in 30 (58.8%) pts; most cases did not require dose modification. Grade ≥3 infections occurred in 23 (45.1%) pts, mostly in cycle 1. The general incidence of febrile neutropenia and infections decreased with subsequent cycles. Four (7.8%) pts died due to unrelated TEAEs: bronchopulmonary aspergillosis, pneumonia, pulmonary sepsis, and possible intracranial hemorrhage after a fall. TEAEs leading to dose reduction (5.9%) or dose interruption (11.8%) were infrequent.

In TN AML, complete remission (CR)/CR with partial hematologic recovery (CRh) was achieved in 16 (59.3%) and CR in 13 (48.1%) evaluable pts (**Table 1**). Of the 13 pts in CR, 7 (53.8 %) reached CR by end of cycle 1. In cohort 2 with the longest follow-up, CR was achieved in 8 (72.7%) pts with TN AML. Notably, 7 of these pts are continuing study treatment (median of 5 cycles, range 1-12) without progression. In R/R AML, CR/CRh was seen in 50% of evaluable pts, with a CR rate of 25%. Nine (50.0%; 6 TN, 3 R/R) of 18 evaluable pts with CR/CRh achieved MRD negativity (<0.1% per ELN 2018).

In pts with AML treated with 40, 80, and 160 mg, PK increased in a dose-dependent manner at steady state with no drug-drug interaction observed with aza.

Conclusion: These results demonstrate that BGB-11417 in combination with aza was effective and generally well tolerated at the 4 dose levels tested in pts with AML, with no dose-dependent toxicities observed. Further evaluation of the 28-day regimen is underway.

Table 1: Baseline Characteristics and Best Overall Response in Patients With AML By Investigator Assessment

Baseline characteristics[a]	TN				R/R				Total	
	Cohort 1 40 mg x 10 d (n=9)	Cohort 2 80 mg x 10 d (n=11)	Cohort 3 160 mg x 10 d (n=7)	Cohort 4 160 mg x 28 d (n=1)	Cohort 1 40 mg x 10 d (n=7)	Cohort 2 80 mg x 10 d (n=6)	Cohort 3 160 mg x 10 d (n=7)	Cohort 4 160 mg x 28 d (n=3)	TN (N=28)	R/R (N=23)
Male, n (%)	6 (66.7)	5 (45.5)	5 (71.4)	1 (100)	3 (42.9)	3 (50.0)	4 (57.1)	3 (100)	17 (60.7)	13 (56.5)
Age, median (range), years	72 (64-91)	77 (67-85)	76 (70-87)	78 (78-78)	64 (36-80)	70 (54-78)	54 (42-71)	63 (54-69)	76.5 (64-91)	64 (36-80)
De novo AML, n (%)	6 (66.7)	11 (100)	6 (85.7)	0	7 (100)	4 (66.7)	6 (85.7)	3 (100)	23 (82.1)	20 (87.0)
AML risk, n (%)										
Intermediate	4 (44.4)	5 (45.5)	1 (14.3)	1 (100)	3 (42.9)	1 (16.7)	3 (42.9)	1 (33.3)	11 (39.3)	8 (34.8)
Adverse	5 (55.6)	3 (27.3)	3 (42.9)	0	3 (42.9)	4 (66.7)	3 (42.9)	2 (66.7)	11 (39.3)	12 (52.2)

Efficacy[b]	TN				R/R				Total	
	Cohort 1 40 mg x 10 d (n=9)	Cohort 2 80 mg x 10 d (n=11)	Cohort 3 160 mg x 10 d (n=6)	Cohort 4 160 mg x 28 d (n=1)	Cohort 1 40 mg x 10 d (n=6)	Cohort 2 80 mg x 10 d (n=6)	Cohort 3 160 mg x 10 d (n=5)	Cohort 4 160 mg x 28 d (n=3)	TN (N=27)	R/R (N=20)
ORR[c], n (%) [95% CI]	6 (66.7) [29.9, 92.5]	10 (90.9) [58.7, 99.8]	4 (66.7) [22.3, 95.7]	0 [0.0, 97.5]	5 (83.3) [35.9, 99.6]	4 (66.7) [22.3, 95.7]	2 (40) [5.3, 85.3]	2 (66.7) [9.4, 99.2]	20 (74.1) [53.7, 88.9]	13 (65) [40.8, 84.6]
CR/CRh, n (%)	4 (44.4)	8 (72.7)	4 (66.7)	0	3 (50.0)	3 (50.0)	2 (40.0)	2 (66.7)	16 (59.3)	10 (50.0)
CR	3 (33.3)	8 (72.7)	2 (33.3)	0	2 (33.3)	2 (33.3)	1 (20.0)	0	13 (48.1)	5 (25.0)
CR after 1 cycle	2 (66.7)	4 (50.0)	1 (50.0)	0	0	0	0	0	7 (53.8)	0
Time to CR, median, months	1.3	1.8	2.5	N/A	3.3	4.2	1.9	N/A	1.4	3.8

AML, acute myeloid leukemia; CR, complete remission; CRh, CR with partial hematologic recovery (*Blood Rev* 2018;32[5]:416-25); N/A, not applicable; ORR, overall response rate; R/R, relapsed/refractory; TN, treatment-naïve.

[a]Included all patients who received at least 1 dose of study drugs.

[b]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. One TN and 3 R/R patients have not yet completed the first cycle and were excluded from the efficacy analysis set.

[c]ORR included CR, CR with incomplete hematologic recovery, morphologic leukemia-free state, and partial remission.

Table 2: Summary of TEAEs, DLT, and Hematologic TEAEs of Clinical Interest

Safety[a]	BGB-11417				
	40 mg x 10 d (n=16)	80 mg x 10 d (n=17)	160 mg x 10 d (n=14)	160 mg x 28 d (n=4)	Total (N=51)
BGB-11417 duration of treatment, median (range), months	1.84 (0.3-7.4)	6.01 (0.3-12.3)	1.12 (0.1-6.7)	1.61 (0.0-2.4)	1.94 (0.0-12.3)
DLTs, n (%)	0	2 (13.3)	0	0	2 (3.9)
Grade ≥3 TEAEs, (n%)	16 (100)	15 (88.2)	12 (85.7)	4 (100)	47 (92.2)
Neutropenia[b]	9 (56.3)	13 (76.5)	6 (42.9)	2 (50.0)	30 (58.8)
Thrombocytopenia[c]	7 (43.8)	8 (47.1)	6 (42.9)	2 (50.0)	23 (45.1)
Serious TEAEs[d]	12 (75.0)	13 (76.5)	11 (78.6)	2 (50.0)	38 (74.5)
TEAEs at any grade					
Leading to BGB-11417 discontinuation[e], n (%)	2 (12.5)	2 (11.8)	1 (7.1)	2 (50.0)	7 (13.7)
Leading to death	1 (6.3)	2 (11.8)	0	1 (25.0)	4 (7.8)
Mortality at 30 days[f]	1 (6.3)	0	0	0	1(1.9)
Leading to cycle delay	9 (56.3)	13 (76.5)	5 (35.7)	2 (50.0)	29 (56.9)
Neutropenia	6 (37.5)	10 (58.8)	4 (28.6)	2 (50.0)	22 (43.1)
Thrombocytopenia	1 (6.3)	2 (11.8)	2 (14.3)	1 (25.0)	6 (11.8)
Leading to dose interruption[g]	0	5 (29.4)	1 (7.1)	0	6 (11.8)
Neutropenia	0	3 (17.6)	0	0	3 (5.9)
Thrombocytopenia	0	0	1 (7.1)	0	1 (2.0)
Leading to dose reduction of BGB-11417[h]	1 (6.3)	1 (5.9)	1 (7.1)	0	3 (5.9)
Neutropenia	1 (6.3)	0	1 (7.1)	0	2 (3.9)
Thrombocytopenia	0	0	0	0	0

DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

[a]Safety evaluable set include all patients who received at least 1 dose of study drug.

[b]Baseline grade ≥3 neutropenia in 68.8% (40 mg), 82.3% (80 mg), 71.4% (160 mg x 10 d); 50% (160 mg x 28 d) of patients.

[c]Baseline grade ≥3 thrombocytopenia in 56.3% (40 mg), 47% (80 mg), 64.3% (160 mg x 10 d); 25% (160 mg x 28 d) of patients.

[d]Most common serious TEAE: febrile neutropenia (27.5%).

[e]TEAEs leading to BGB-11417 discontinuation: bacterial sepsis, bronchopulmonary aspergillosis, pneumonia, pulmonary sepsis, septic shock, anemia, thrombocytopenia, and possible intracranial hemorrhage due to mechanical fall (all unrelated to study drugs, except for septic shock and thrombocytopenia).

[f]TEAEs leading to death within 30 days of starting study treatment: pulmonary sepsis.

[g]TEAEs leading to dose interruption: neutropenia, thrombocytopenia, bronchopulmonary aspergillosis, vascular device infection, and acute kidney injury.

[h]TEAEs leading to BGB-11417 dose reduction: neutropenia and febrile neutropenia