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

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]School of Clinical Sciences, Monash University and Monash Health, Clayton, VIC, Australia; [2]Hospital Politecnico Universitario La Fe, Valencia, Spain; [3]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [4]Gold Coast University Hospital, Southport, QLD, Australia; [5]Austin Health, Heidelberg, VIC, Australia; [6]Fiona Stanley Hospital, Murdoch, WA, Australia; [7]North Shore Hospital, Auckland, New Zealand; [8]One Clinical Research, Nedlands, WA, Australia; [9]The Saint George Hospital-Kogarah, Kogarah, NSW, Australia; [10]Concord Repatriation General Hospital, Concord West, NSW, Australia; [11]Orange Health Service (Central West Cancer Care Centre), Orange, NSW, Australia; [12]Department of Clinical Haematology, The Alfred Hospital, Prahran, VIC, 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, WA, Australia; [15]Peking University People's Hospital, Beijing, China; [16]University of Texas MD Anderson Cancer Center, Houston, TX, 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, VIC, Australia

Disclosure information for Dr. Emma Searle

Dr. Emma Searle (The Christie Hospital NHS Foundation Trust and The University of Manchester) is presenting on behalf of the authors

Honoraria from Abbvie and Janssen; consulting or advisory role with Shattuck Labs; travel expenses from Janssen and Abbvie.

Introduction

- The efficacy of Bcl-2 inhibitors with hypomethylating agents for treating patients with 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, BGB-11417 showed greater tumor reduction than venetoclax at the same dose level, alone and 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 treated with BGB-11417 + azacitidine in BGB-11417-103 (NCT04771130)

AML, acute myeloid leukemia; Bcl-2, B-cell lymphoma 2.

1. DiNardo CD, et al. *N Engl J Med.* 2020;383(7):617-629; 2. Hu N, et al. *Cancer Res.* 2020;80(suppl 16):3077; 3. Data on file. BGB-11417 Investigator Brochure; 4. Opat S, et al. EHA 2022. Abstract P687; 5. Shortt J, et al. EHA 2022. Abstract P590.

Study Design

- 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) and with MDS

Eligibility Criteria

- Aged ≥18 years
- AML (non-APL)
- TN unfit for intensive chemotherapy
- R/R with no prior Bcl-2 inhibitor or azacitidine exposure
- ECOG PS 0-2
- Not receiving warfarin; moderate or strong CYP3A4 inhibitor or inducer within 5 half-lives

BGB-11417 (10 days or 28 days in 28-day cycle with 4-day ramp up in cycle 1 starting at 1/8 of the target dose[a])
+
Azacitidine (75 mg/m^2 for 7 days SC or IV)

Part 1 Dose Escalation → **Part 2** Safety Expansion → RP2D → **Part 3** Efficacy Expansion

BGB-11417 dose	Part 1	Part 2
40 mg x 10 days	3-6 patients	~10 patients
80 mg x 10 days	3-6 patients	~10 patients
160 mg x 10 days	3-6 patients	~10 patients
160 mg x 28 days	3-6 patients	~10 patients

Part 3
~20 patients

[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.
AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; Bcl-2, B-cell lymphoma 2; CYP3A4, cytochrome P450 3A4; EGOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MDS, myelodysplastic syndrome; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SC, subcutaneous; TN, treatment naïve.
1. Howard SC, et al. *N Engl J Med.* 2011;364(19):1844-1854; Erratum in: *N Engl J Med.* 2018;379(11):1094.

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

AML, acute myeloid leukemia; CR, complete response; CRh, complete response with partial hematologic recovery; PK, pharmacokinetics; RP2D, recommended phase 2 dose.

DLT and Response Assessment

- DLTs were assessed in cycle 1
  - Patients were DLT evaluable if they received ≥80% the intended cumulative dose in cycle 1

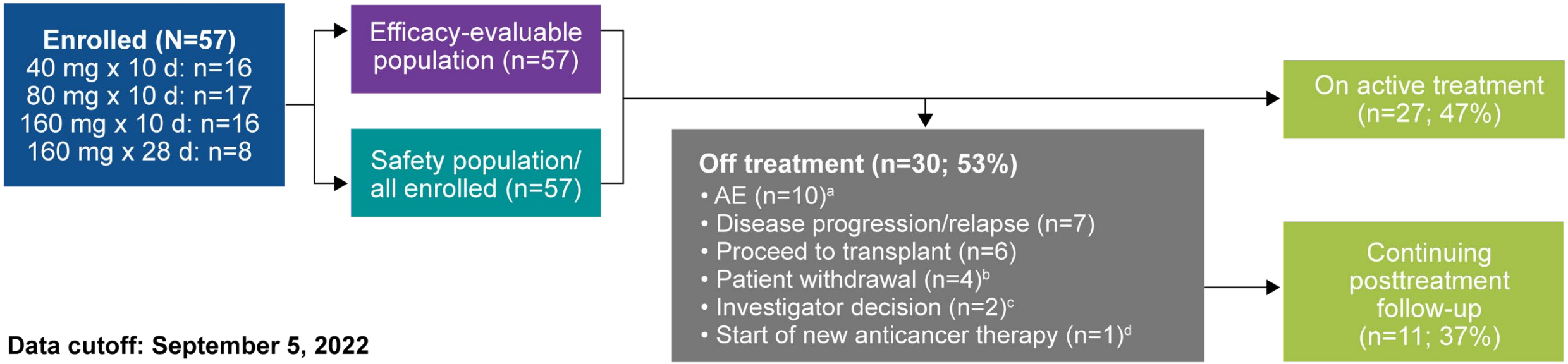
- Response assessments based on European LeukemiaNet 2017 Response Criteria with assessment of hematologic improvement[1,2] were performed every 3 cycles starting at the end of cycle 1
  - For patients not in remission, an additional response assessment was performed at the end of cycle 2
- MRD status was assessed by multiparameter flow cytometry[3] at the end of cycles 1 and 4, and at the end of cycle 2 if additional response assessment was performed

d, day; DLT, dose-limiting toxicity; MRD, minimal residual disease.

1. Bloomfield CD, et al. *Blood Rev.*2018;32(5):416-425; 2. Döhner H, et al. *Blood* 2017;129(4):424-447; 3. Schuurhuis GJ, et al. *Blood* 2018;131(12):1275-1291.

Patient Disposition

- 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)



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.
AE, adverse events; d, day.

Baseline Demographics And 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.
AML, acute myeloid leukemia; R/R, relapsed/refractory; TN, treatment naïve.

Treatment Exposure in AML

Dose	40 mg x 10 days (n=16)		80 mg x 10 days (n=17)		160 mg x 10 days (n=16)		160 mg x 28 days (n=8)		Total (N=57)	
Treatment	**BGB-11417**	**Aza**	**BGB-11417**	**Aza**	**BGB-11417**	**Aza**	**BGB-11417**	**Aza**	**BGB-11417**	**Aza**
Median duration of treatment (min, max), months	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), days	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)	

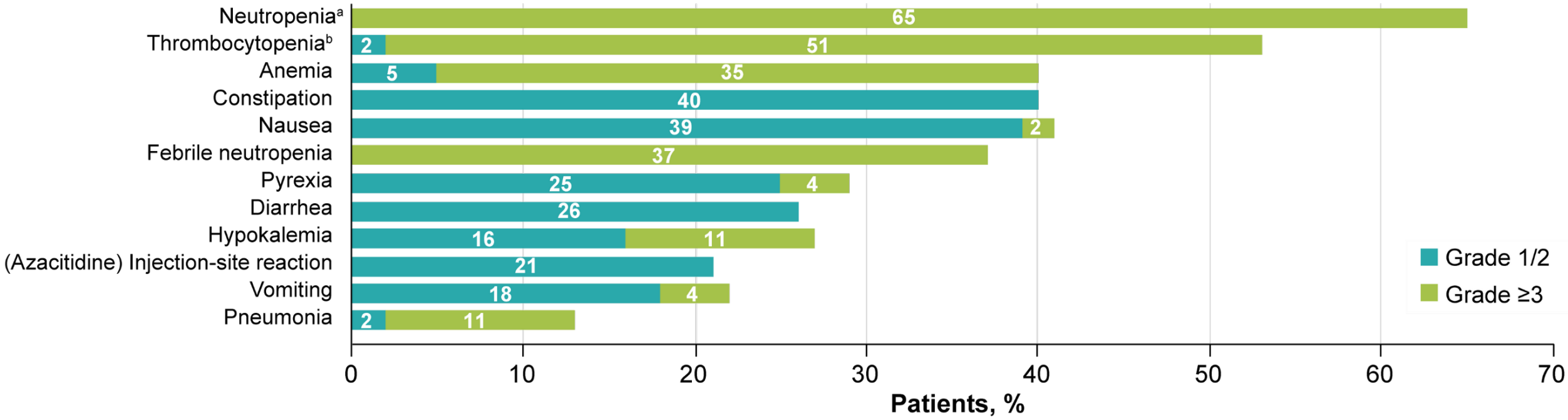
[a]Each cycle duration should be 28 days. If initiation of the following cycle is delayed for any reason, the cycle duration will be measured up to the last day before the next cycle was initiated or treatment discontinuation, whichever occurred first.
Aza, azacytidine; d, days.

Safety

TEAEs, n(%)	Total (N=57)
Any TEAE	57 (100)
Grade ≥3	53 (93)
Serious	46 (81)
Leading to death[a]	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)

[a]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).
AML, acute myeloid leukemia; COPD, chronic obstructive pulmonary disease; d, days; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event; TN, treatment naïve.

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.
TEAE, treatment-emergent adverse event.

DLTs and TLS

DLT Evaluable[a], n (%)	BGB-11417				
	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

- 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
- No clinical TLS was observed; laboratory TLS occurred in a patient treated with 160 mg x 10 days (assessed based on Howard criteria[1])[b]

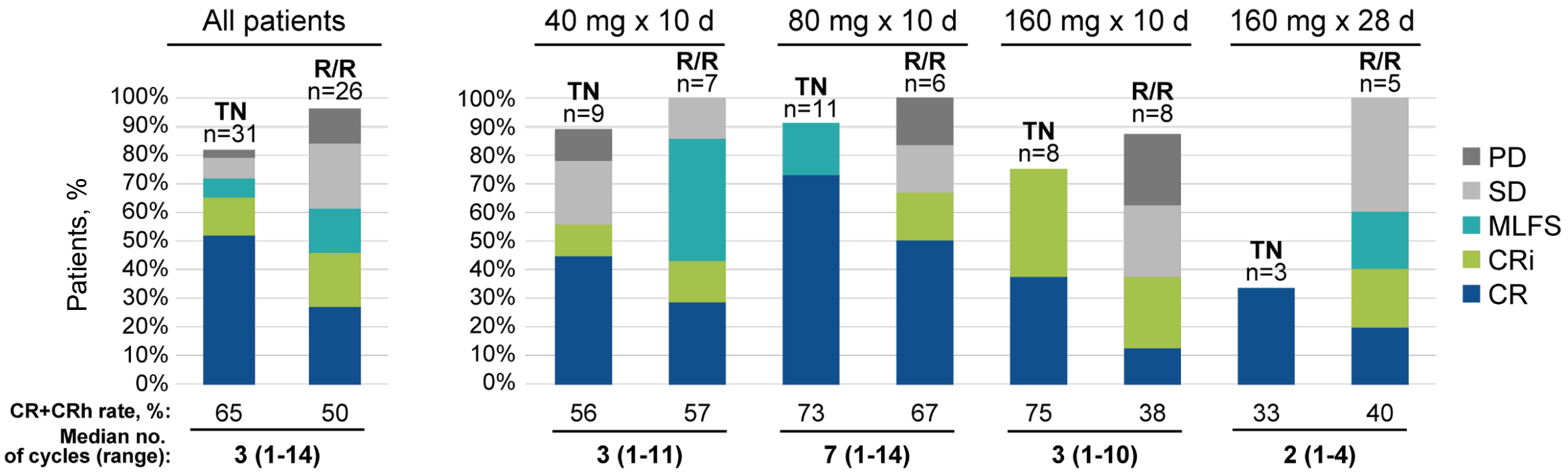
[a]Based on DLT evaluable set, which includes patients who completed the DLT observation window and received ≥80% of the intended cumulative dose. [b]This patient had pre-existing history of chronic kidney disease. He was managed successfully as an outpatient and fully recovered after 4 days.
d, days; DLT, dose-limiting toxicity, TLS, tumor lysis syndrome.
1. Howard SC, et al. *N Engl J Med* .2011;364(19):1844-1854; Erratum in: *N Engl J Med.* 2018;379(11):1094.

Efficacy

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,[a] 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)

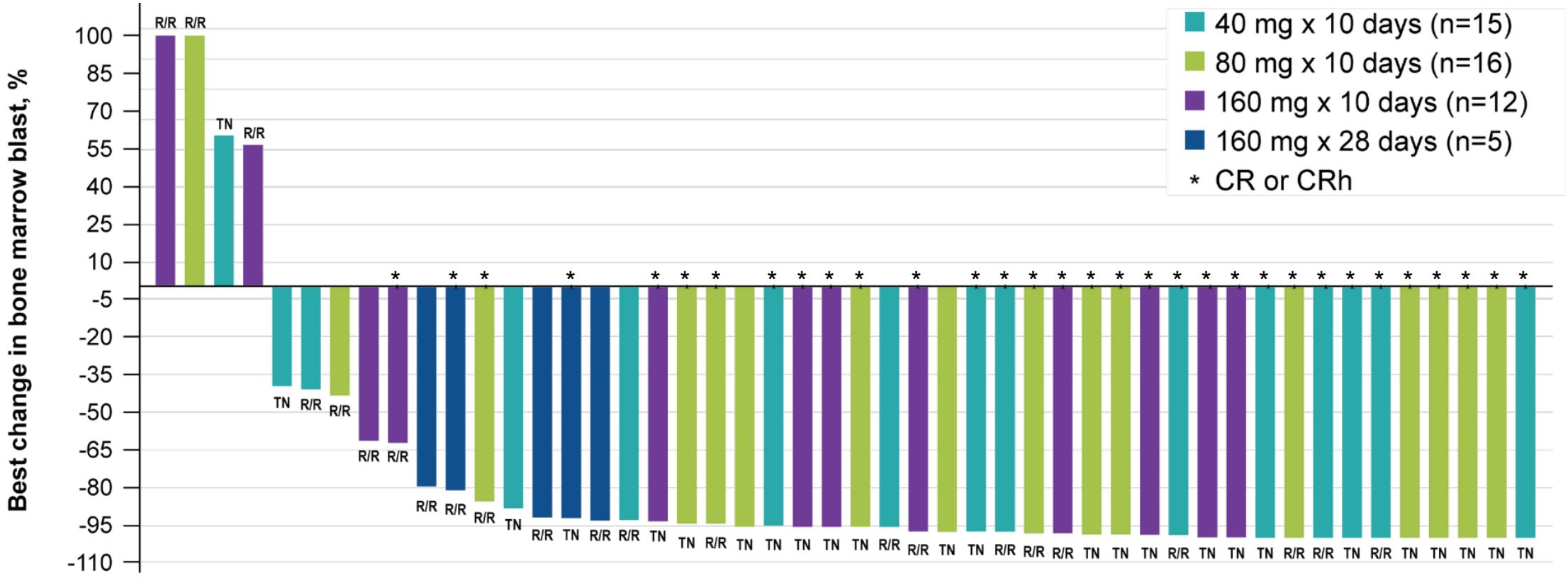
[a]CRh was defined by Bloomfield et al.[1]
Response assessments based on 2017 ELN response criteria with assessment of hematologic improvement (part 3).[1, 2]
Number of patients who did not have a posttreatment response assessment: in TN 40 mg and 80 mg (n=1 each), in TN 160 mg x 10 days and x 28 days (n=2 each), and in R/R 160 mg x 10 days (n=1).
CR, complete response; CRh, complete response with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; d, days; R/R, relapsed/refractory; TN, treatment naïve.
1. Bloomfield CD, et al. *Blood Rev.* 2018;32(5):416-425; 2. Döhner H, et al. *Blood* 2017;129(4):424-447.

Best Overall Response



Patients with best overall response of Not Done or Not Evaluable are not shown in the bar graph.
CR, complete response; CRh, complete response with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; MLFS, morphological leukemia-free state; PD, progressive disease; R/R, relapsed/refractory; SD, stable disease; TN, treatment naïve.

Best Change From Baseline in Bone Marrow Blasts



CR, complete response; CRh, complete response with partial hematologic recovery; R/R, R/R, relapsed/refractory; TN, treatment naïve.

1. Schuurhuis GJ, et al. *Blood* 2018;131(12):1275-1291.

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 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

Acknowledgements

The authors would like to thank the investigators, site support staff, and especially the patients for participating in this study.

This study was sponsored by BeiGene. Editorial support was provided by Medical Expressions.