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Preliminary Safety and Efficacy of BGB-11417, A Potent and Selective B-Cell Lymphoma 2 (Bcl-2) Inhibitor, In Patients With Acute Myeloid Leukemia (AML)

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Disclosures for Jose Antonio Perez Simon

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Introduction

- BCL2, a key apoptosis regulator, is aberrantly expressed in many hematologic malignancies
- Venetoclax-based treatments have improved outcomes in patients with AML who are unfit for induction chemotherapy
  - Disease resistance/relapse and GI/hematological toxicities remain[1]
- BGB-11417 is a potent and highly selective investigational Bcl-2 inhibitor
  - Superior antitumor activity compared with venetoclax in preclinical studies[2]
  - Favorable PK profile and excellent bioavailability and selectivity for Bcl-2 (< 1 nM)[2]
    - 2,000-fold higher selectivity for Bcl-2 than Bcl-xL[2]
  - Well tolerated at doses up to 640 mg in a phase 1 monotherapy study[3]
- The safety and efficacy of BGB-11417 + azacitidine in patients with AML were evaluated in the ongoing BGB-11417-103 study

AML, acute myeloid leukemia; Bcl-2, B-cell lymphoma 2; GI, gastrointestinal; PK, pharmacokinetics.
1. DiNardo C, et al. *N Engl J Med.* 2020;383(7):617-629; 2. Hu N, et al. *Cancer Res.* 2020;80(suppl 16):3077; 3. Opat S, et al. EHA 2022. Abstract P687.

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

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 concurrent CYP3A4 inhibitor or inducer

BGB-11417
(10 days or 28 days with 4-day ramp up in cycle 1)
+
Azacitidine
(75 mg/m² for 7 days SC or IV)

Part 1[a] Dose Escalation → Part 2 Safety Expansion → RP2D → Part 3 Efficacy Expansion

BGB-11417 Dose	Part 1	Part 2
40 mg x 10 days	n = 3-6	n ~10
80 mg x 10 days	n = 3-6	n ~10
160 mg x 10 days	n = 3-6	n ~10
160 mg x 28 days	n = 3-6	n ~10

Part 3
n ~20

Primary Objective

- Safety and tolerability of BGB-11417 + azacitidine, determine RP2D (parts 1 - 2) and efficacy (ELN 2017 Response Criteria; part 3)[1,2]

Secondary Objective

- PK of BGB-11417 + azacitidine

Exploratory Objective

- Biomarker characteristics and correlation with efficacy

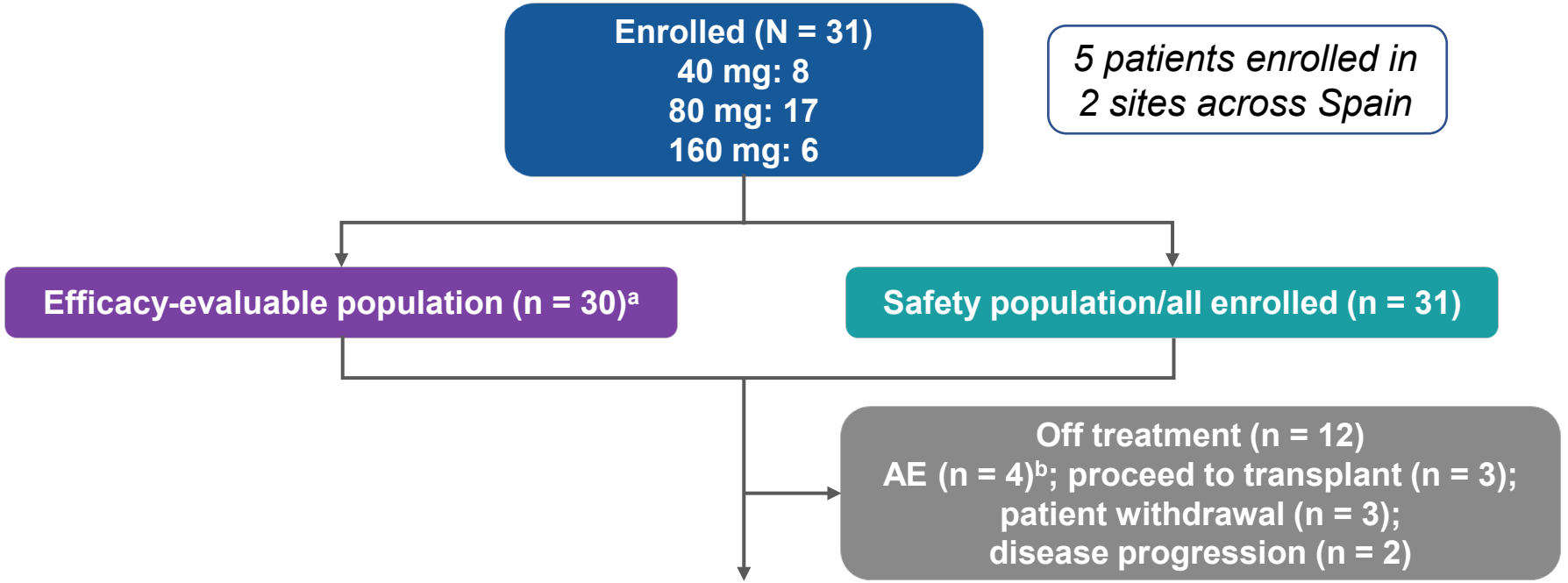
[a]Safety Monitoring Committee reviews available patient safety and preliminary efficacy data to determine dose escalation in part 1, dose expansion to part 2, and the final RP2D to start part 3.
AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; Bcl-2, B-cell lymphoma 2; CR, complete response; CRh, CR with partial hematologic recovery; CYP3A4, cytochrome P450 3A4; ECOG PS, Eastern Cooperative Oncology Group performance status; ELN, European LeukemiaNet; IV, intravenous; PK, pharmacokinetics; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; SC, subcutaneous; TN, treatment naive.
1. Döhner H, et al. *Blood.* 2017;129(4):424-447; 2. Bloomfield C, et al. *Blood Rev.* 2018;32(5):416-425.

Methods

- Tumor lysis syndrome precautions with hospitalization during the ramp-up period
- DLTs were assessed in cycle 1
  - DLTs were assessed against the number of patients dosed
  - 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 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 at the end of cycles 1 and 4

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

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

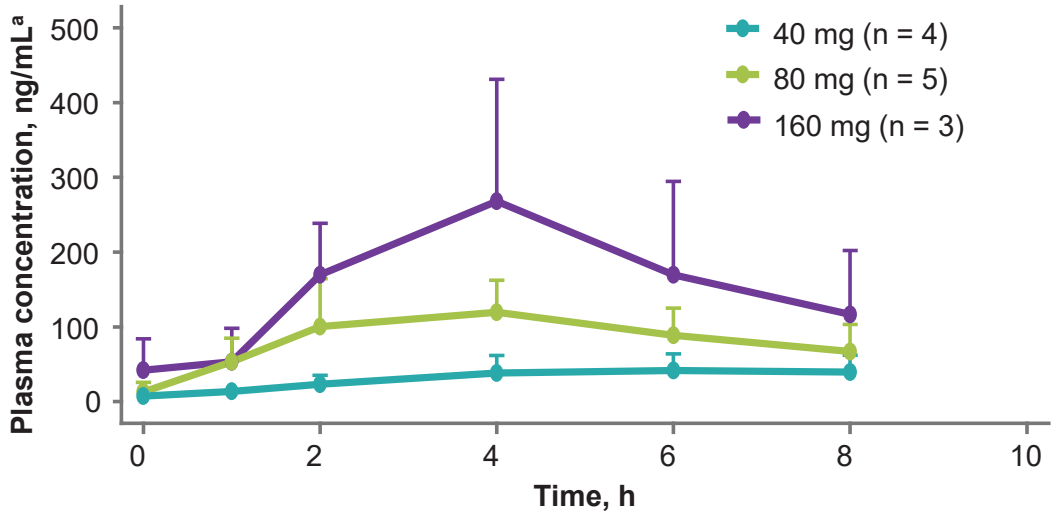
[a]The efficacy evaluable set included patients who completed at least 1 cycle of treatment (ie, initiated the second cycle) or 42 days, whichever is earlier, or discontinued treatment during the first cycle; [b]AE leading to treatment discontinuations: infections (bacterial sepsis, pulmonary sepsis,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

Baseline Characteristics

Characteristics	TN (n = 19)	R/R (n = 12)	All (N = 31)
Age, median (range), years	80 (64-87)	69 (36-78)	74 (36-87)
Female, 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)	14 (45.2)

AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; R/R, relapsed/refractory; TN, treatment naive.

Steady State Plasma Concentration Profile of BGB-11417



PK parameters	40 mg (n = 4)	80 mg (n = 5)	160 mg (n = 3)
T_{max}, median (range), hours	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)

- The estimated terminal half-life is approximately 5 hours[b]
- Steady state C_{max} and AUC_{0-8} appeared to increase in a dose-dependent manner
- Steady state C_{max} and AUC_{0-8} of BGB-11417 in combination with azacitidine were comparable to that of BGB-11417 monotherapy

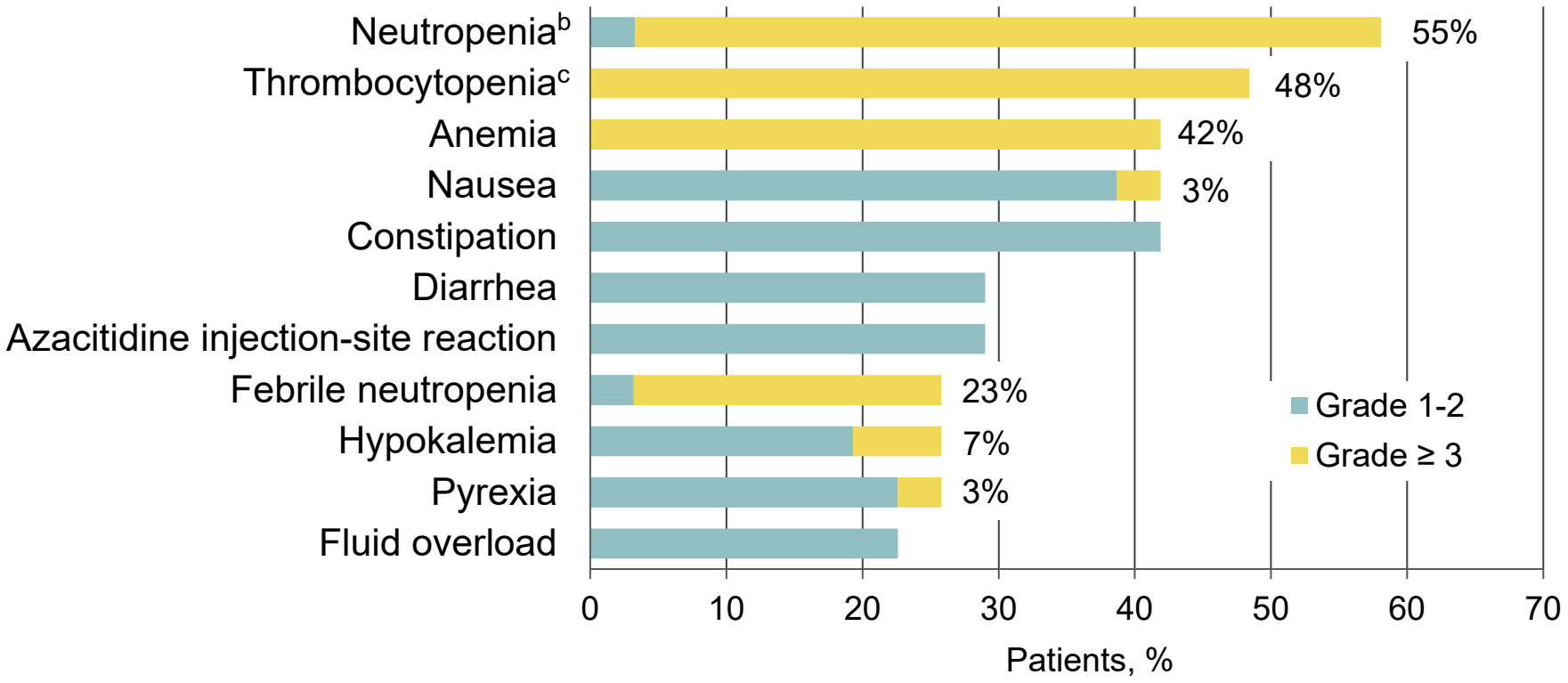
[a]Error bars indicate standard deviation; [b]Based on PK data from monotherapy cohorts in Phase 1 study BGB-11417-101.
AUC, area under the curve; C_{max}, maximum concentration; PK, pharmacokinetics; T_{max}, time to maximum concentration.

TEAE Summary

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)[e]

[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).
AML, acute myeloid leukemia; TEAE, treatment-emergent adverse event.

Most Common TEAEs[a] (≥ 20% for All Grades)



[a]TEAEs were assessed according to NCI-CTCAE (v5.0); [b]12 (38.7%) led to cycle delay, 1 (3.2%) to study drug interruption, 1 (3.2%) required dose reduction; among 17 patients with Grade ≥ 3 neutropenia, 7 (41.2%) had serious infections and 5 (29.4%) had febrile neutropenia; [c]2 (6.5%) led to cycle delay, 1 (3.2%) to study drug interruption.
NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.

Dose-Limiting Toxicity and Tumor Lysis Syndrome

	BGB-11417			
	40 mg × 10 days (n = 5)	80 mg × 10 days (n = 15)	160 mg × 10 days (n = 6)	Total[b] (N = 26)
DLT, n (%)[a]	0	2 (13.3)	0	2 (7.7)
Hematologic	0	2 (13.3)	0	2 (7.7)
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, n (%)[c]	0	0	1 (16.7)[d]	1 (3.2)

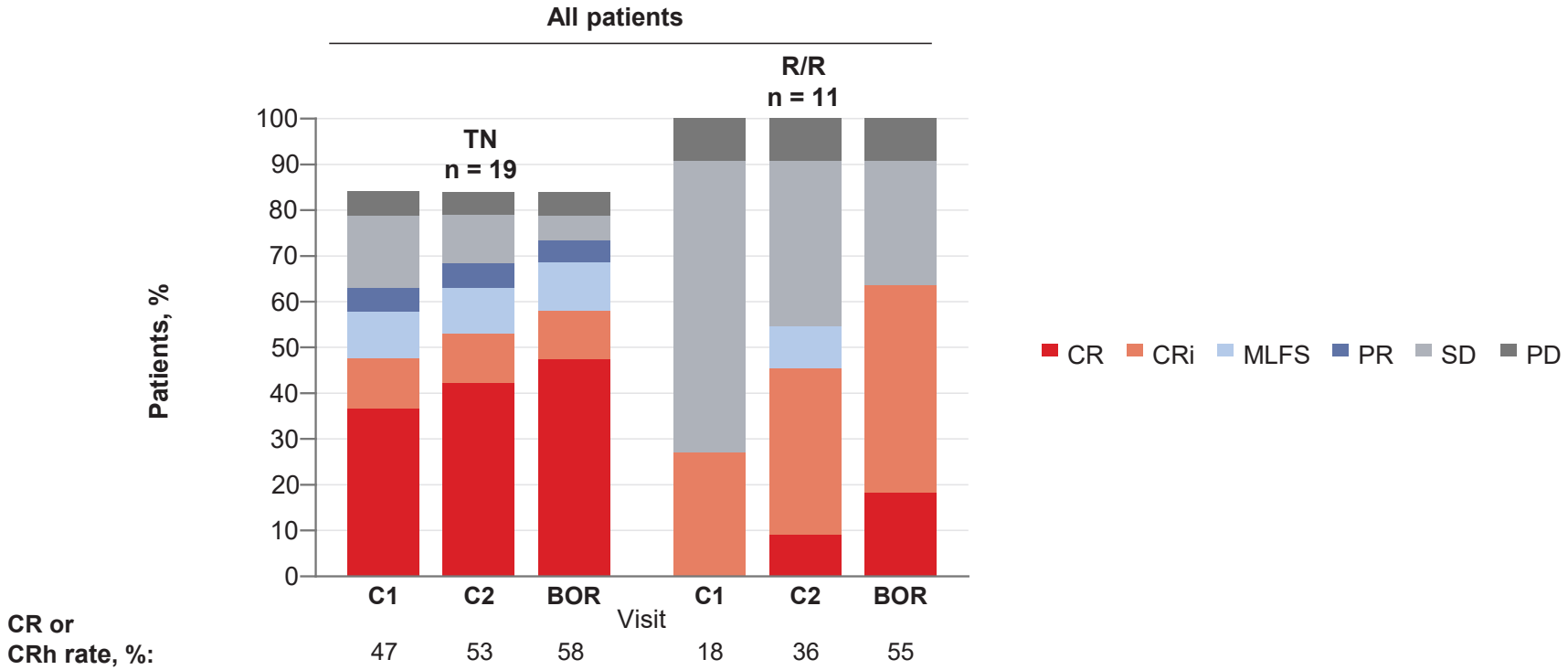
[a]DLT was assessed through cycle 1 day 28 (nonhematologic) and up to day 42 or initiation of cycle 2 (hematologic); [b]Based on DLT evaluable set, which includes patients who completed the DLT observation window and received ≥ 80% of the intended cumulative dose; [c]TLS assessment based on the Howard criteria[1]; [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.
DLT, dose-limiting toxicity; TLS, tumor lysis syndrome.
1. Howard C, et al. *N Engl J Med.* 2011;364(19):1844-1854. Erratum in: *N Engl J Med.* 2018;379(11):1094.

Best Overall Response

	40 mg × 10 days		80 mg × 10 days		160 mg × 10 days		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)**
ORR (CR + CRi + MLFS + PR), n (%)	2 (50)	2 (67)	10 (91)	3 (50)	2 (50)	2 (100)	14 (74)	7 (64)
CR + CRh, n (%)	2 (50)	2 (67)	7 (64)	2 (33)	2 (50)	2 (100)	11 (58)	6 (55)
CR + CRi, n (%)	2 (50)	2 (67)	7 (64)	3 (50)	2 (50)	2 (100)	11 (58)	7 (64)
CR	2 (50)	0	6 (55)	1 (17)	1 (25)	1 (50)	9 (47)	2 (18)
Time to CR, median, months	1.31	N/A	1.36	3.75	0.95	1.94	1.31	2.84
BGB-11417 treatment duration, median (range), months	1.31 (0.3-4.8)		2.96 (0.3-9.2)		1.95 (0.3-3.7)		2.40 (0.3-9.2)	

CR, complete response; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial response; R/R, relapsed/refractory; TN, treatment naive.

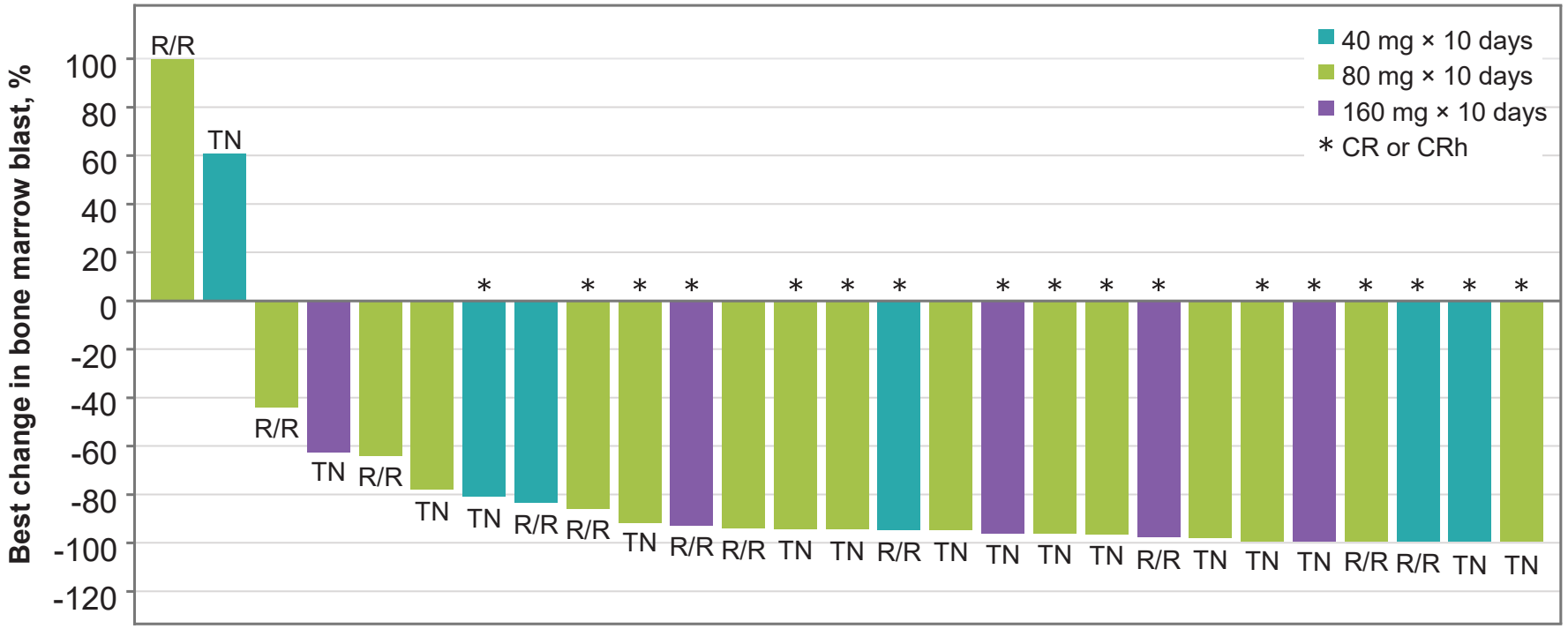
Best Overall Response Over Time



- Most CRs were achieved by the end of cycle 1

BOR, best overall response; C, cycle; CR, complete response; CRh, CR with partial hematologic recovery; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment naive.
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.

Best Change from Baseline in Bone Marrow Blasts



- Most patients had ≥ 80% reduction in bone marrow blasts

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

Conclusions

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

[a]Grade 4 neutropenia/thrombocytopenia.

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