Interim Safety Analysis of Zanubrutinib in Japanese Patients With Mature B-Cell Malignancies

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BeiGene

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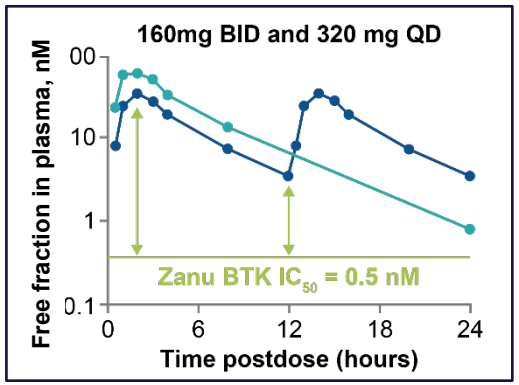
Disclosures

- **Masahiro Takeuchi** has no disclosures to report
- This research has received IRB approval at the Chiba Cancer Center and each clinical trial site

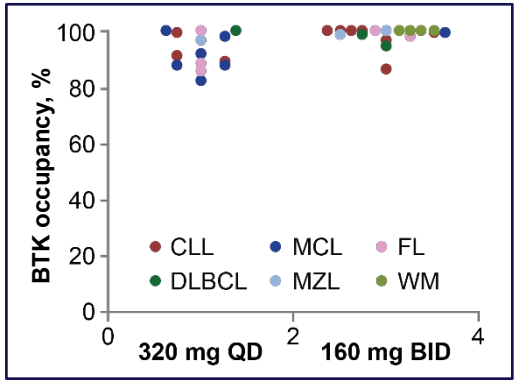
Zanubrutinib

- Zanubrutinib (BGB-3111) is a potent, irreversible, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target kinase inhibition[1-3]

	Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
ON TARGET	BTK	BTK-pY223 Cellular Assay	1.8	3.5	0.5
		Rec-1 Proliferation	0.36	0.34	1.1
		BTK Occupation Cellular Assay	2.2	2.3	1.0
		BTK Biochemical Assay	0.22	0.2	1.1
OFF TARGET	EGFR	p-EGFR HTRF Cellular Assay	606	101	6
		A431 Proliferation	3210	323	9.9
	ITK	ITK Occupancy Cellular Assay	3265	189	17
		p-$PLC_{\gamma1}$ Cellular Assay	3433	77	45
		IL-2 Production Cellular Assay	2536	260	9.8
		ITK Biochemical Assay	30	0.9	33
	JAK3	JAK3 Biochemical Assay	200	3.9	51
	HER2	HER2 Biochemical Assay	661	9.4	70
	TEC	TEC Biochemical Assay	1.9	0.8	2.4
	CSK	CSK Biochemical Assay	218	4.5	48



C_{max} and C_{trough} > BTK IC_{50} over 24 hours



Complete and sustained BTK occupancy

BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CSK, C-terminal Src kinase; DLBCL, diffuse large B cell lymphoma; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; HER2, human epidermal growth factor receptor 2; ITK, interleukin-2-inducible T-cell kinase; JAK3, janus kinase 3; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; TEC, Tec protein tyrosine kinase; QD, once daily; WM, Waldenström macroglobulinemia.

1. Guo Y, et al. *J Med Chem* 2019;62:7923-40. 2. Tam CS, et al. *Blood* 2019;134:851-9. 3. Tam CS, et al. *Blood* 2015;126(23):832.

Zanubrutinib Efficacy and Safety

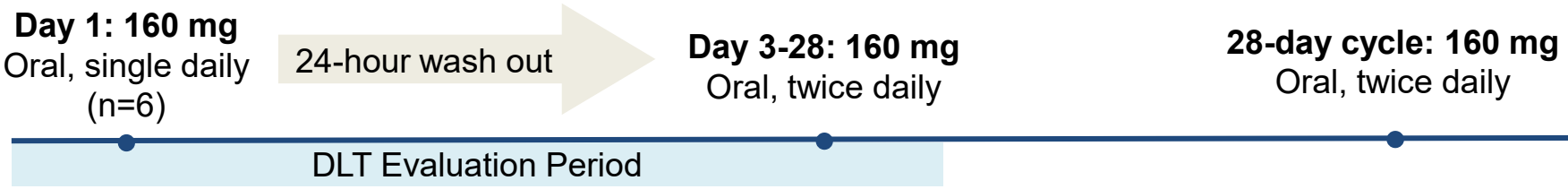
- Zanubrutinib has shown efficacy and safety in multiple global phase 2 and 3 studies
  - Superior response rate, improved PFS, and a lower rate of atrial fibrillation/flutter compared with ibrutinib in patients with relapsed/refractory CLL/SLL in the interim analysis of phase 3 ALPINE study[1]
  - Higher quality of response, fewer AEs leading to death, treatment discontinuation, or dose reduction compared with ibrutinib in patients with WM with 44-month follow-up in the phase 3 ASPEN study[2,3]
  - High response rate (ORR 83.7%, CR 77.9%) and extended PFS (median 33.0 months) in patients with relapsed/refractory MCL with a median follow-up of 35.3 months in the phase 2 BGB-3111-206 study[4]
  - Currently under investigation as a potential treatment in combination with rituximab compared with bendamustine plus rituximab for patients with previously untreated MCL who are ineligible for SCT in the phase 3 MANGROVE study[5]

AE, adverse event; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; PFS, progression-free survival; SCT, stem cell transplantation; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

1. Hillmen P, et al. EHA 2021. 2. Tam CS, et al. *Blood* 2020;136(18):2038-50. 3. Tam CS, et al. ASCO 2022. 4. Song Y, et al. *Blood* 2022;139(21):3148-58. 5. Dreyling M, et al. *Future Oncol* 2021;17(3):255-62.

BGB-3111-111: A Phase 1/2 Study of Zanubrutinib in Japanese Patients With Mature B-Cell Malignancies

Part 1: Confirmation of Safety, Tolerability, and Pharmacokinetics in Japanese Patients



Primary Objective

- To evaluate the safety and tolerability of zanubrutinib at 160 mg orally twice daily
- To evaluate the pharmacokinetic profile of a single dose of zanubrutinib at 160 mg orally and multiple doses of zanubrutinib at 160 mg orally twice daily

Part 2: Efficacy, Safety, and Tolerability in Disease-Specific Cohorts

Disease Type	R/R MCL	TN CLL/SLL	R/R CLL/SLL	R/R or TN WM
Target enrollment	10	5-12	5-12	16-19
Enrollment as of July 24, 2021	8	11	2	19

Primary Objective

- To assess the efficacy of zanubrutinib as measured by ORR determined by IRC

CLL, chronic lymphocytic leukemia; DLT, dose-limiting toxicity; IRC, independent review committee; MCL, mantle cell lymphoma; ORR, overall response rate; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment naïve; WM, Waldenström macroglobulinemia.

Demographic and Baseline Characteristics

Characteristics	Part 1 (n = 6)	Part 2 (n = 40)	Overall (N = 46)
Indications, n			
R/R MCL	1	8	9
TN WM	0	13	13
R/R WM	2	6	8
R/R FL	2	0	2
R/R MZL	1	0	1
TN CLL/SLL	0	11	11
R/R CLL/SLL	0	2	2
Median age (range), years	68.5 (47-84)	70.5 (37-83)	69.5 (37-84)
<65 years, n (%)	2 (33.3)	10 (25.0)	12 (26.1)
≥65 years, n (%)	4 (66.7)	30 (75.0)	34 (73.9)
Sex, n (%)			
Male, n (%)	5 (83.3)	26 (65.0)	31 (67.4)
Female, n (%)	1 (16.7)	14 (35.0)	15 (32.6)
ECOG PS, n (%)			
0	4 (66.7)	30 (75.0)	34 (73.9)
1	2 (33.3)	9 (22.5)	11 (23.9)
2	0	1 (2.5)	1 (2.2)

Data cutoff: July 24, 2021.
CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment naïve; WM, Waldenström macroglobulinemia.

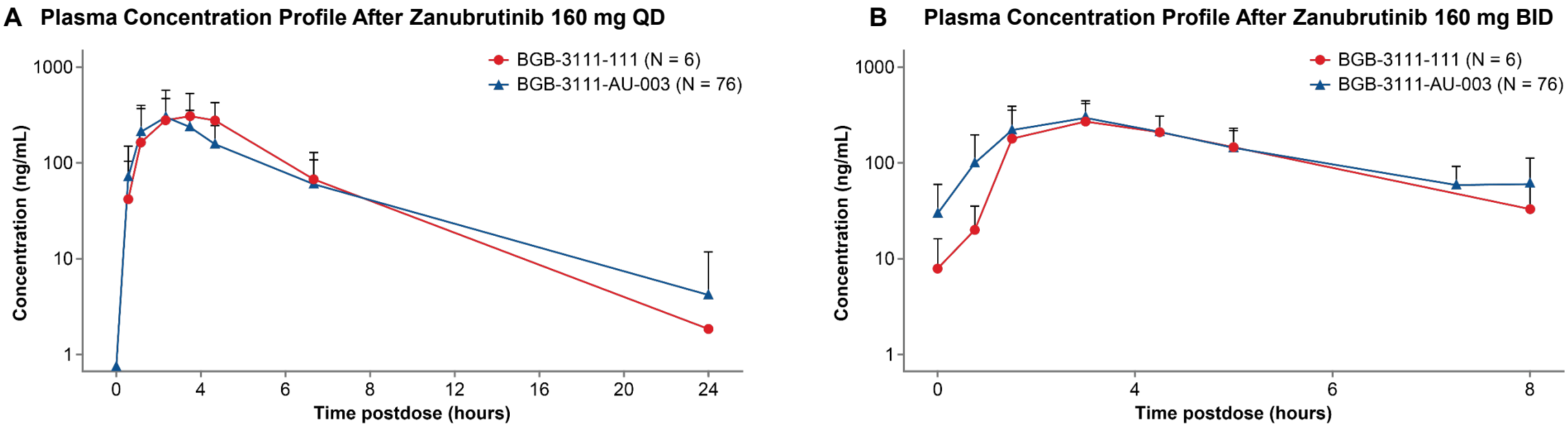
Patient Disposition and Exposure

	Part 1 (n = 6)	Part 2 (n = 40)	Overall (N = 46)
Treatment duration, median (range), months	10.1 (2.1-16.9)	5.5 (0.5-10.9)	6.0 (0.5-16.9)
Study follow-up time, median (range), months	16.1 (13.1-17.8)	5.5 (0.6-10.9)	6.5 (0.6-17.8)
Discontinued treatment, n (%)	4 (66.7)	3 (7.5)	7 (15.2)
Progressive disease	4 (66.7)	2 (5.0)	6 (13.0)
Investigator decision	0 (0.0)	1 (2.5)	1 (2.2)
Discontinued from study, n[a] (%)	1 (16.7)	1 (2.5)	2 (4.3)
Dose reduction, n (%)	1 (16.7)	1 (2.5)	2 (4.3)
Other (due to use of CYP3A inhibitor)	1 (16.7)	1 (2.5)	2 (4.3)
Patients with dose interruption, n (%)	2 (33.3)	6 (15.0)	8 (17.4)
Held for procedure	0 (0.0)	2 (5.0)	2 (4.3)
Investigator decision	2 (33.3)	2 (5.0)	4 (8.7)
Adverse event	0 (0.0)	3 (7.5)	3 (6.5)

[a]Discontinued due to death from progressive disease.
CYP3A, cytochrome P450, family 3, subfamily A.
Data cutoff: July 24, 2021.

Plasma Exposure of Zanubrutinib

- The exposure of zanubrutinib in Japanese patients (BGB-3111-111) was comparable to exposures observed in published zanubrutinib trials at equivalent doses (BGB-3111-AU-003)



Plasma concentration profiles show arithmetic mean (+SD) for the 24-hour pharmacokinetic evaluation on (A) day 1 of cycle 1 and (B) day 1 of cycle 2. Zanubrutinib plasma concentrations on *Y*-axis are shown in logarithmic scale.
BID, twice daily; QD, once daily; SD, standard deviation.

Summary of Treatment-Emergent Adverse Events

TEAEs, n (%)	Part 1 (n = 6)	Part 2 (n = 40)	Overall (N = 46)
Subjects with ≥1 TEAE	6 (100.0)	30 (75.0)	36 (78.3)
Treatment related	5 (83.3)	17 (42.5)	22 (47.8)
Serious TEAE	2 (33.3)	3 (7.5)	5 (10.9)
Treatment related	0 (0.0)	1 (2.5)	1 (2.2)
Grade ≥3	4 (66.7)	10 (25.0)	14 (30.4)
Treatment related	3 (50.0)	4 (10.0)	7 (15.2)
Leading to death	0 (0.0)	0 (0.0)	0 (0.0)
Leading to treatment discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Leading to dose modification	0 (0.0)	3 (7.5)	3 (6.5)
Leading to dose reduction	0 (0.0)	0 (0.0)	0 (0.0)
Leading to drug interruption	0 (0.0)	3 (7.5)	3 (6.5)
TEAEs of special interest	4 (66.7)	17 (42.5)	21 (45.7)

- Within the first 28-day period for DLT assessment, there were no DLTs observed in the 6 patients from Part 1
- No AEs leading to deaths or treatment discontinuation occurred

Data cutoff: July 24, 2021.
AE, adverse event; DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

Most Common AEs and Treatment-Related Grade ≥3 TEAEs

Most Common AEs in ≥3 Patients[a]

Preferred term, n (%)	Part 1 (n = 6)	Part 2 (n = 40)	Overall (N = 46)
Platelet count decreased	3 (50.0)	3 (7.5)	6 (13.0)
Neutrophil count decreased	2 (33.3)	2 (5.0)	4 (8.7)
Constipation	1 (16.7)	3 (7.5)	4 (8.7)
Purpura	1 (16.7)	2 (5.0)	3 (6.5)
Anemia	2 (33.3)	1 (2.5)	3 (6.5)
Neutropenia	1 (16.7)	2 (5.0)	3 (6.5)
Arthralgia	1 (16.7)	2 (5.0)	3 (6.5)
Pyrexia	2 (33.3)	1 (2.5)	3 (6.5)
Decreased appetite	0 (0.0)	3 (7.5)	3 (6.5)
Hypertension	0 (0.0)	3 (7.5)	3 (6.5)

Treatment-Related Grade ≥3 TEAEs[b]

Preferred term, n (%)	Part 1 (n = 6)	Part 2 (n = 40)	Overall (N = 46)
Patients with at least 1 grade ≥3 treatment-related TEAE	3 (50.0)	4 (10.0)	7 (15.2)
Neutrophil count decreased	1 (16.7)	2 (5.0)	3 (6.5)
Neutropenia	1 (16.7)	2 (5.0)	3 (6.5)
Febrile neutropenia	0 (0.0)	1 (2.5)	1 (2.2)
Platelet count decreased	1 (16.7)	0 (0.0)	1 (2.2)
White blood cell count decreased	0 (0.0)	1 (2.5)	1 (2.2)
Pneumonia cryptococcal	0 (0.0)	1 (2.5)	1 (2.2)
Drug eruption	1 (16.7)	0 (0.0)	1 (2.2)

Data cutoff: July 24, 2021.
[a]Patients with multiple events for a given preferred term were counted only once at the worst grade for the preferred term. AEs were classified based on MedDRA Version 24.0.
[b]AE grades were evaluated based on iwCLL 2018 Grading Scale for hematologic toxicity for patients with CLL/SLL. Otherwise, AE grades were evaluated based on NCI-CTCAE Version 5.0.
AE, adverse event; CLL, chronic lymphocytic leukemia; iwCLL, International Workshop on CLL; MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for AEs; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event.

TEAEs of Special Interest

TEAE, n (%)	Part 1 (n = 6)	Part 2 (n = 40)	Overall (N = 46)
Patients with ≥1 TEAE of special interest	4 (66.7)	17 (42.5)	21 (45.7)
Hemorrhage[a]	1 (16.7)	8 (20.0)	9 (19.6)
Infections	2 (33.3)	7 (17.5)	9 (19.6)
Opportunistic infections	0 (0.0)	1 (2.5)	1 (2.2)
Neutropenia[b]	3 (50.0)	4 (10.0)	7 (15.2)
Thrombocytopenia[c]	3 (50.0)	4 (10.0)	7 (15.2)
Anemia	2 (33.3)	1 (2.5)	3 (6.5)
Hypertension	0 (0.0)	3 (7.5)	3 (6.5)
Second primary malignancies	0 (0.0)	2 (5.0)	2 (4.3)
Skin cancers	0 (0.0)	1 (2.5)	1 (2.2)

Data cutoff: July 24, 2021.
TEAE, treatment-emergent adverse event.
[a] Includes 3 purpura and 2 petechiae. No grade 3 events.
[b] Includes neutropenia and neutrophil count decreased.
[c] Includes thrombocytopenia and platelet count decreased.

Conclusions

- At data cutoff of July 24, 2021, the BGB-3111-111 study enrolled 46 Japanese patients with B-cell malignancies (n=6 Part 1; n=40 Part 2)
- This study enrolled a majority (93.5%) of patients with WM, CLL/SLL, and R/R MCL
- No patients in Part 1 experienced dose-limiting toxicities
- The plasma exposure of zanubrutinib was comparable to that observed in published zanubrutinib trials at equivalent doses
- The pharmacokinetics of zanubrutinib were comparable to those observed across ethnic groups
- Preliminary safety data were consistent with the safety profile reported in zanubrutinib trials
- Preliminary results suggest that zanubrutinib was well tolerated in Japanese patients with mature B-cell malignancies

CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

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Dose-Limiting Toxicity Criteria

- The period for dose-limiting toxicity assessment is 28 days from the first dose of zanubrutinib in Part 1

Hematologic

- Grade 4 neutropenia >10 days
- Grade ≥3 neutropenia with fever or infection
  - The use of growth factor support to avoid a dose-limiting toxicity of neutropenia is not permitted
- Grade 4 thrombocytopenia >10 days
- Grade ≥3 thrombocytopenia with clinically significant bleeding
  - Grade 3 or higher thrombocytopenia requiring transfusion will be considered a dose-limiting toxicity

Non-hematologic

- Grade ≥3 atrial fibrillation associated with hemodynamic instability
- Grade ≥3 hemorrhage
- Grade ≥3 opportunistic infection
- Any-grade ≥2 nonhematological toxicity resulting in ≥14 days of study drug interruption in a cycle, or permanent treatment discontinuation

Source: BGB-3111-111 Protocol Amendment 2.0