Efficacy and Safety of Zanubrutinib in Japanese Patients With Mature B-Cell Malignancies

Abstract 1590

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INTRODUCTION

- Zanubrutinib is a potent and selective irreversible next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target kinase inhibition and associated AEs[1,2]
- Zanubrutinib is approved globally for the treatment of B-cell malignancies in adults[3-5]
- BGB-3111-111 (NCT04172246) is an ongoing, multicenter, open-label phase 1/2 study to assess the safety and efficacy of zanubrutinib in Japanese patients with mature B-cell malignancies
- Here, we present investigator-assessed efficacy and safety data from patients in the BGB-3111-111 study

METHODS

Key Inclusion Criteria

- Patients with a confirmed diagnosis of mature B-cell neoplasms, including CLL/SLL, MCL, FL, MZL, and WM
- Measurable disease by CT/MRI for patients with MCL, MZL, and FL and by serum IgM level >0.5 g/dL for patients with WM

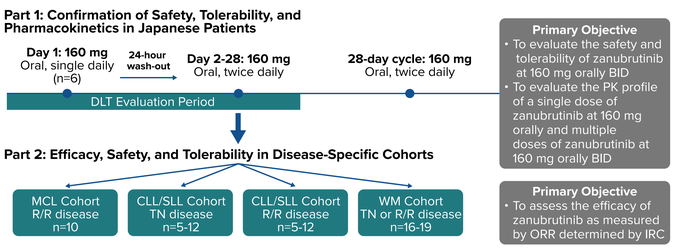
Key Exclusion Criteria

- Prior allogeneic stem cell transplant, systemic chemotherapy or radiation therapy within 2 weeks prior to first dose of zanubrutinib
- Prior therapy with B-cell receptor inhibitor (eg, BTK, PI3Kδ, and/or SYK inhibitor) or Bcl-2 inhibitor (eg, venetoclax/ABT-199)

Response Assessment

- Responses were assessed by investigators based on the Lugano Classification for MCL (PET- and CT-/MRI-based) and SLL (CT-/MRI-based),[6] 2018 iwCLL guidelines with modification for treatment-related lymphocytosis for CLL,[7] and WM response criteria updated at the 6th International Workshop on WM[8]

Figure 1. BGB-3111-111 Study Design



RESULTS

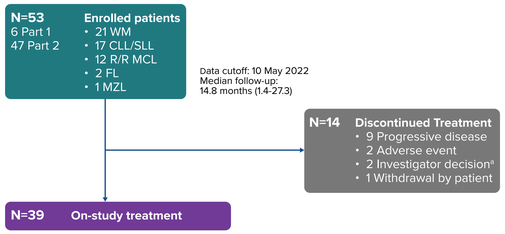
Table 1. Patient Demographics and Baseline Characteristics

Characteristics	Part 1 (n=6)	Part 2 (n=47)	Overall (N=53)
Indications, n (%)			
WM	2 (33.3)	19 (40.4)	21 (39.6)
TN CLL/SLL	0	14 (29.8)	14 (26.4)
R/R CLL/SLL	0	3 (6.4)	3 (5.7)
R/R MCL	1 (16.7)	11 (23.4)	12 (22.6)
FL	2 (33.3)	0	2 (3.8)
MZL	1 (16.7)	0	1 (1.9)
Median age (range), years	68.5 (47-84)	71 (37-83)	71 (37-84)
Sex, n (%)			
Male, n	5 (83.3)	31 (66.0)	36 (67.9)
Female, n	1 (16.7)	16 (34.0)	17 (32.1)
ECOG PS, n (%)			
0	5 (83.3)	37 (78.7)	42 (79.2)
≥1	1 (16.7)	10 (21.3)	11 (20.8)
Prior lines of therapy for R/R patients, median (range), n (%)	5 (1-6)	1 (1-8)	2 (1-8)

Data cutoff: 10 May 2022.

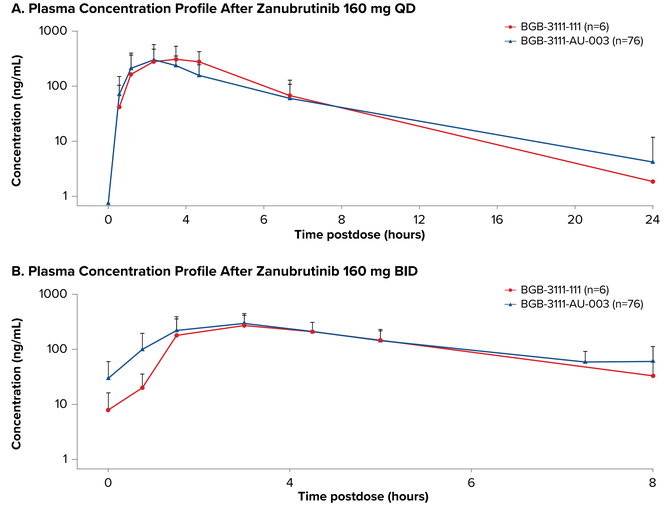
RESULTS

Figure 2. Patient Disposition and Exposure



[a]One patient discontinued to prioritize treatment for angiosarcoma. One patient discontinued due to noncompliance with the study drug.

Figure 3. Plasma Exposure of Zanubrutinib



Plasma concentration profiles show arithmetic mean (+ standard deviation) for the 24-hour PK 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.

- 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)[9]
- The early difference in 160 mg BID concentration may likely be due to high variability and small sample size

Table 2. Summary of Adverse Events

AEs, n (%)	Total N=53
Serious AEs	13 (24.5)
Fatal AEs	1 (1.9)[a]
AEs leading to dose interruption	14 (26.4)
AEs leading to dose reduction	2 (3.8)
AEs leading to treatment discontinuation	2 (3.8)

Data cutoff: 10 May 2022.
[a]One patient with R/R MCL experienced a fatal TEAE of septic shock.

Table 3. Most Common Any Grade and Grade ≥3 Adverse Events

AEs, n (%)	Total N=53
Any AE	48 (90.6)
Most common AEs[a]	
Platelet count decreased	10 (18.9)
Pyrexia	7 (13.2)
Neutrophil count decreased	6 (11.3)
Anemia	5 (9.4)
Back pain	5 (9.4)
Constipation	5 (9.4)
Decreased appetite	5 (9.4)
Hypertension	5 (9.4)
Purpura	5 (9.4)
Arthralgia	4 (7.5)
Headache	4 (7.5)
Any grade ≥3 AE[b]	22 (41.5)
Neutrophil count decreased	5 (9.4)
Platelet count decreased	5 (9.4)
Neutropenia	3 (5.7)

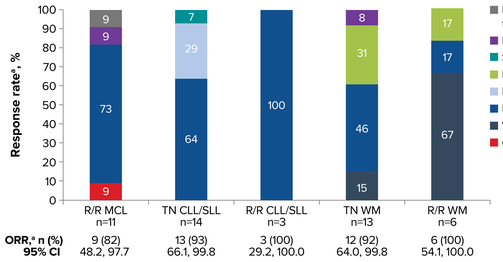
Data cutoff: 10 May 2022.
[a]Occurring in ≥4 patients any grade. [b]Occurring in ≥3 patients ≥grade 3.

Table 4. TEAEs of Special Interest

TEAEs, n (%)	Overall (N=53) Any grade	Overall (N=53) Grade ≥3
Patients with ≥1 TEAE of special interest[a]	35 (66.0)	17 (32.1)
Hemorrhage[b]	21 (39.6)	5 (9.4)
Major hemorrhage[c]	5 (9.4)	5 (9.4)
Infections	17 (32.1)	6 (11.3)
Opportunistic infections	1 (1.9)	1 (1.9)
Thrombocytopenia[d]	11 (20.8)	5 (9.4)
Neutropenia[e]	9 (17.0)	8 (15.1)
Anemia	5 (9.4)	1 (1.9)
Hypertension	5 (9.4)	1 (1.9)
Second primary malignancies	4 (7.5)	4 (7.5)
Skin cancers	2 (3.8)	2 (3.8)

Data cutoff: 10 May 2022.
[a]No patient reported ventricular arrhythmias. [b]Including terms of 5 purpura, 3 conjunctival hemorrhage, and 3 petechiae. [c]Combined terms of gastric hemorrhage, hyphema, post procedural hemorrhage, traumatic intracranial hemorrhage, and tumor hemorrhage. [d]Combined terms of thrombocytopenia and platelet count decreased. [e]Combined terms of neutropenia, neutrophil count decreased, and febrile neutropenia.

Figure 4. Investigator-Assessed Overall Response



Data cutoff: 10 May 2022.
*The overall response rate is defined as PR or better for MCL; PR-L or better for CLL/SLL; MR or better for WM.

- Median duration of response and median PFS have not been reached for any disease cohort

CONCLUSIONS

- The plasma 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)[9-14]
- Zanubrutinib was shown to be highly active in Japanese patients with WM, CLL/SLL, and R/R MCL
- Investigator-assessed efficacy data in Japanese patients were comparable with the efficacy of zanubrutinib seen in global zanubrutinib studies[9-14]
- Zanubrutinib was generally well tolerated in Japanese patients with B-cell malignancies
- Preliminary safety and efficacy data from this phase 1/2 study support the use of zanubrutinib as a treatment option for Japanese patients with WM, CLL/SLL, and R/R MCL

REFERENCES

1. Guo et al. *J Med Chem* 2019;62(17):7923-7940
2. Shadman et al. *Lancet Haematol* Forthcoming 2022
3. BRUKINSA [package insert]. San Mateo, USA. BeiGene USA, Inc. Sept 2021
4. BRUKINSA [product monograph]. BeiGene Switzerland GmbH. February 2021
5. Zanubrutinib; National Medical Products Administrations; 2021
6. Cheson et al. *J Clin Oncol* 2014;32(27):3059-3068
7. Hallek et al. *Blood* 2008;111(12):5446-5456
8. Owen et al. *Br J Haematol* 2013;160(2):171-176
9. Takeuchi et al. SH 2022. Abstract OS3-6B-5
10. Tam et al. *Lancet Oncol* 2022;23(8):1031-1043
11. Hillmen et al. EHA 2021. Abstract LB1900
12. Tam et al. *Future Oncol* 2018;14(22):2229-2237
13. Song et al. *Blood* 2022;139(21):3148-3158
14. Tam et al. *Blood Adv* 2022;6(4):1296-1308

ABBREVIATIONS

AE, adverse event; BCL2, B-cell lymphoma 2; BID, twice daily; BTK, Bruton tyrosine kinase; CI, confidence interval; CLL, chronic lymphocytic leukemia; CR, complete response; CT, computed tomography; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IgM, immunoglobulin M; IRC, independent review committee; iwCLL, International Workshop on CLL; MCL, mantle cell lymphoma; MR, minor response; MRI, magnetic resonance imaging; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PI3Kδ, phosphoinositide 3 kinase delta; PK, pharmacokinetic; PR, partial response; PR-L, partial response with lymphocytosis; QD, once daily; R/R, relapsed or refractory; SD, stable disease; SLL, small lymphocytic lymphoma; SYK, spleen tyrosine kinase; TEAE, treatment-emergent adverse event; TN, treatment-naive; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

DISCLOSURES

KSh: consultancy with Chugai, Daiichi Sankyo, BMS, AbbVie, Novartis, Meiji Seika; research funding from Celgene, Chugai, Kyowa Kirin, Daiichi Sankyo, Otsuka, Eisai; honoraria from Celgene, BMS, Eisai, Chugai, Novartis, Daiichi Sankyo, AstraZeneca, Janssen, Takeda, Symbio, Asclepia.

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HG, WN, CT, HY, HZ: employment and equity with BeiGene Ltd.

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JZ: employment and equity with BeiGene (Shanghai), Co. Ltd.

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TI, MaTa, KK, KF, TF, KN, SKu, TJ, SKa, TN: nothing to disclose.

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