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Pooled Safety Analysis of Zanubrutinib Monotherapy in Asian Patients With B-Cell Malignancies

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COI disclosure

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I currently have, or I have had in the past two years, an affiliation or financial interest with business corporation(s):

(1) Consulting fees, patent royalties, licensing fees :	**No**
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Background

- In patients with B-cell malignancies, continuous treatment with ibrutinib, a first-generation BTK inhibitor, is often limited due to toxicities that may be associated with inhibition of off-target kinases[1]
- Zanubrutinib is a potent and selective next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target effects; it is approved in the US, EU, and China for the treatment of various B-cell malignancies in adults[2-5]
- Here, pooled safety data from 10 clinical trials are presented from 406 Asian patients with various B-cell malignancies who were treated with zanubrutinib

BTK, Bruton tyrosine kinase.

1. Estupiñán HY, et al. *Front Cell Dev Biol*. 2021;9:630942; 2. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940; 3. Brukinsa (zanubrutinib). Package insert. BeiGene USA, Inc; 2023; 4. Brukinsa (zanubrutinib). Product monograph. Beigene Switzerland GmbH; 2021; 5. Gale RP. *Chin Med J (Engl)*. 2022;135(8):883-886.

Methods

- A post hoc analysis of pooled safety data from Asian patients in 10 clinical trials of zanubrutinib was conducted

Clinical trial	NCT number	Phase	Disease state
BGB-3111-1002	NCT03189524	1	B-cell malignancies (CLL/SLL, MCL, WM, FL, MZL)
BGB-3111-205	NCT03206918	2	CLL/SLL
BGB-3111-206	NCT03206970	2	MCL
BGB-3111-210	NCT03332173	2	WM
BGB-3111-214	NCT03846427	2	MZL
BGB-3111-AU-003	NCT02343120	1/2	B-cell malignancies (CLL/SLL, WM, MCL, MZL, FL, DLBCL, RT, HCL)
BGB-3111-302 (ASPEN)	NCT03053440	3	WM
BGB-3111-304 (SEQUOIA)	NCT03336333	3	CLL/SLL
BGB-3111-305 (ALPINE)	NCT03734016	3	CLL/SLL
BGB-3111-LTE1[a]	NCT04170283	3	B-cell malignancies (enrolled in a BeiGene parent study)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed or refractory; RT, Richter transformation; TN, treatment naive; WM, Waldenström macroglobulinemia.
[a] The 337 patients in this long-term extension study previously participated in one of the other studies and were counted in the parent studies.

Baseline Demographics and Patient Characteristics

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Characteristics	Pooled Asian population (n=406)	Pooled overall population (N=1550)
Age, median (range), years	61.0 (20-87)	67.0 (20-95)
Sex, n (%)		
Male	259 (63.8)	1027 (66.3)
Female	147 (36.2)	523 (33.7)
Race, n (%)		
White	1 (0.2)	1032 (66.6)
Asian	405 (99.8)	424 (27.4)
Other/not reported	0	94 (6.1)
ECOG PS, n (%)		
0	203 (50.0)	692 (44.6)
1	181 (44.6)	763 (49.2)
2	22 (5.4)	95 (6.1)
No. of prior lines of therapy, median (range)[a]	2.0 (1-12)	2.0 (1-12)

Characteristics (cont)	Pooled Asian population (n=406)	Pooled overall population (N=1550)
Diagnosis, n (%)		
CLL/SLL	192 (47.3)	938 (60.5)
WM	47 (11.6)	249 (16.1)
MCL	90 (22.2)	140 (9.0)
MZL	21 (5.2)	93 (6.0)
FL	33 (8.1)	59 (3.8)
DLBCL	23 (5.7)	45 (2.9)
Other	0	26 (1.7)

- The pooled Asian population was younger and had a higher percentage of patients with MCL, FL, and DLBCL compared with the overall population
- Otherwise, the Asian subgroup was representative of the overall group

ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] The n is number of patients with prior lines of therapy/regimens; pooled Asian, n=362 and overall, n=1068.

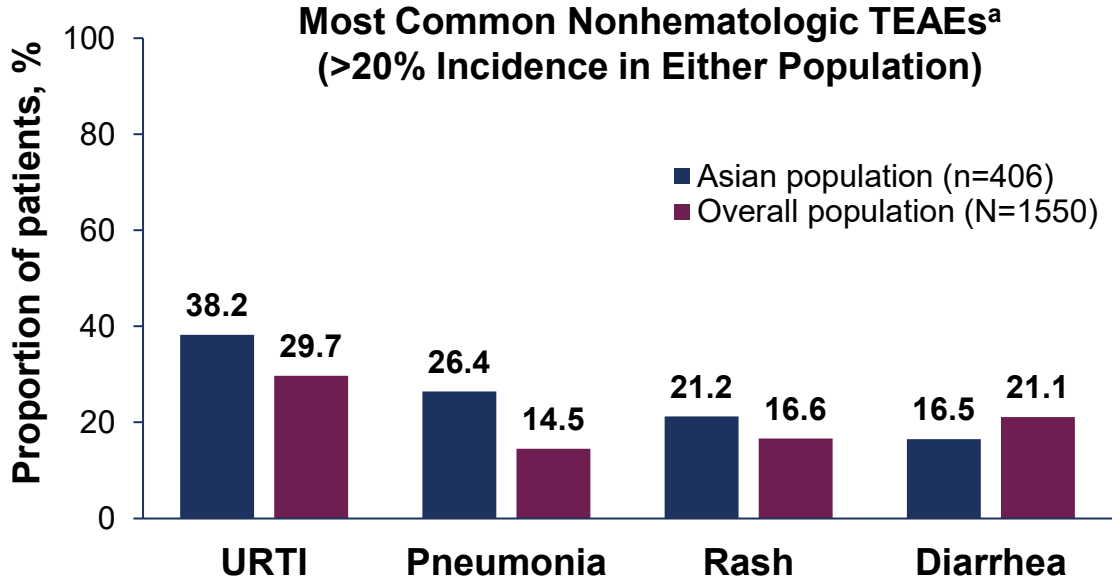
Safety Summary

- Median exposure to zanubrutinib: 25.0 months in the Asian population and 34.4 months in the overall population; 38.7% of Asian patients received treatment for ≥36 months

TEAE summary for the pooled Asian population:

- Most common grade ≥3 TEAEs: pneumonia (16.0%) and anemia (8.1%)
- Only serious TEAE occurring in >10% of patients: pneumonia (14.5%)
- Most common type of TEAE leading to death: infection/infestation (2.0%)
    - Four patients (1.0%) experienced a cardiac disorder-related death

Event, n (%)	Pooled Asian population (n=406)	Pooled overall population (N=1550)
Any TEAE	398 (98.0)	1518 (97.9)
Grade ≥3 TEAE	268 (66.0)	1037 (66.9)
Serious TEAE	178 (43.8)	763 (49.2)
TEAE leading to dose reduction	30 (7.4)	156 (10.1)
TEAE leading to discontinuation	43 (10.6)	211 (13.6)
TEAE leading to death	20 (4.9)	113 (7.3)



TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.
[a] TEAEs were summarized using MedDRA preferred terms.

AESI[a] Incidence Rates and EAIRs

	AESI incidence rates, n (%)		EAIR (person per 100 person-months)	
	Pooled Asian population (n=406)	Pooled overall population (N=1550)	Pooled Asian population (n=406)	Pooled overall population (N=1550)
Any TEAE of special interest	365 (89.9)	1404 (90.6)	–	–
Infections	295 (72.7)	1153 (74.4)	7.42	6.01
Hemorrhage	188 (46.3)	799 (51.5)	2.87	3.00
Major hemorrhage	18 (4.4)	88 (5.7)	0.14	0.17
Neutropenia	213 (52.5)	467 (30.1)	3.64	1.21
Thrombocytopenia	147 (36.2)	274 (17.7)	1.68	0.59
Hypertension	62 (15.3)	259 (16.7)	0.56	0.57
Second primary malignancies	19 (4.7)	248 (16.0)	0.15	0.52
Anemia	116 (28.6)	247 (15.9)	1.14	0.51
Atrial fibrillation/flutter	2 (0.5)	75 (4.8)	0.02	0.15
Tumor lysis syndrome	1 (0.2)	5 (0.3)	0.01	0.01

- Rates of neutropenia, thrombocytopenia, and anemia were higher, but rates of second primary malignancies were lower in the pooled Asian population compared with the overall population
- For both populations, rates of atrial fibrillation were low

AESI, adverse events of special interest; EAIR, exposure-adjusted incidence rate.
[a] AESIs were summarized using pooled terms.

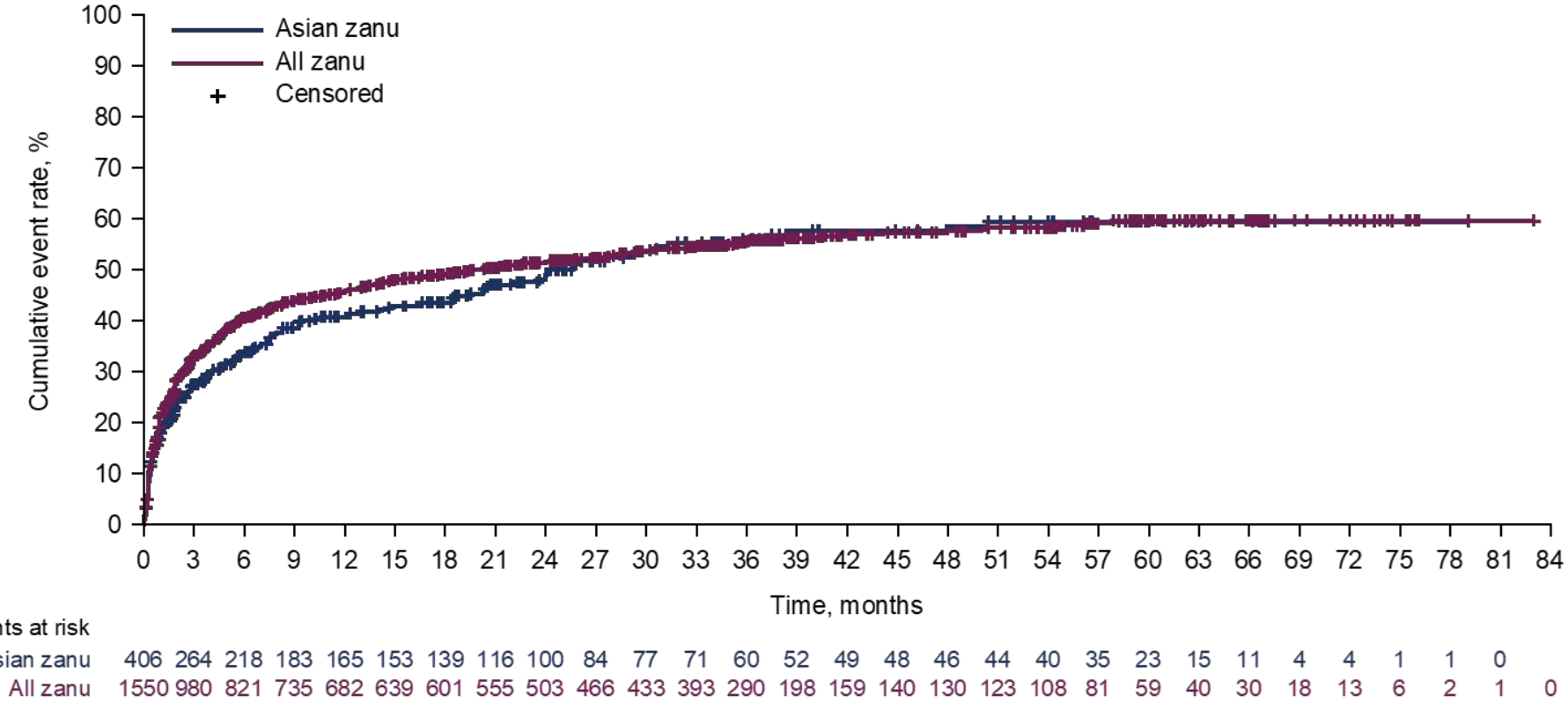
Grade ≥3 AESI[a] Incidence Rates

	Grade ≥3 AESI incidence rates, n (%)	
	Pooled Asian population (n=406)	Pooled overall population (N=1550)
TEAE of special interest	229 (56.4)	847 (54.6)
Infections	126 (31.0)	448 (28.9)
Hemorrhage	15 (3.7)	77 (5.0)
Major hemorrhage	15 (3.7)	77 (5.0)
Neutropenia	121 (29.8)	319 (20.6)
Thrombocytopenia	49 (12.1)	98 (6.3)
Hypertension	18 (4.4)	129 (8.3)
Second primary malignancies	18 (4.4)	112 (7.2)
Anemia	33 (8.1)	88 (5.7)
Atrial fibrillation/flutter	0	31 (2.0)
Tumor lysis syndrome	1 (0.2)	5 (0.3)

- Rates of grade ≥3 neutropenia, thrombocytopenia, and anemia were higher in the pooled Asian population compared with the overall population
- No instances of grade ≥3 atrial fibrillation/flutter occurred in the Asian population

AESI, adverse events of special interest.
[a] AESIs were summarized using pooled terms.

Hemorrhage



- Among 188 patients (46.3%) who reported any grade hemorrhage in the Asian population, 15 patients (3.7%) experienced grade ≥3 hemorrhage during zanubrutinib treatment
- Most hemorrhage events occurred in the first 6 months of zanubrutinib treatment initiation in the Asian population, which is consistent with the overall population
  - Median time to first event in the Asian population: 57.0 days (vs 55.0 days in overall population)
- Dose interruption due to any grade hemorrhage occurred in 16 patients (3.9%)
  - No patients required dose reduction during treatment
- Six patients (1.5%) had withdrawn due to hemorrhage

Conclusions

- Most AEs experienced by patients in zanubrutinib clinical trials were mild to moderate in severity
  - Rates of treatment discontinuation were <15% in both the pooled Asian and overall populations
  - For both populations, rates of atrial fibrillation/flutter were low, and no instances of grade ≥3 atrial fibrillation/flutter occurred in the Asian population
- The overall safety profile of zanubrutinib in Asian patients was consistent with that seen in the overall population with B-cell lymphoma in previous zanubrutinib studies
  - Lower rates of atrial fibrillation/flutter and second primary malignancies, and higher rates of neutropenia, thrombocytopenia, and anemia were seen in the Asian population
- These findings suggest that zanubrutinib is well tolerated in Asian patients with B-cell malignancies

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