Zanubrutinib, a Highly Specific BTK Inhibitor in Chinese Patients with Relapsed/Refractory B-cell Malignancies: Follow-up Report of a Phase 1 Trial in China

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INTRODUCTION

- Bruton's tyrosine kinase (BTK) inhibitors have been demonstrated to be highly active in a variety of B cell malignancies, including Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/ SLL),[1] Mantle Cell Lymphoma (MCL),[2,3] and Waldenström's macroglobulinemia (WM)[4].
- Zanubrutinib (BGB-3111) is an investigational, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases.
- We report here the long-term results of a Phase 1 trial of zanubrutinib in Chinese patients.

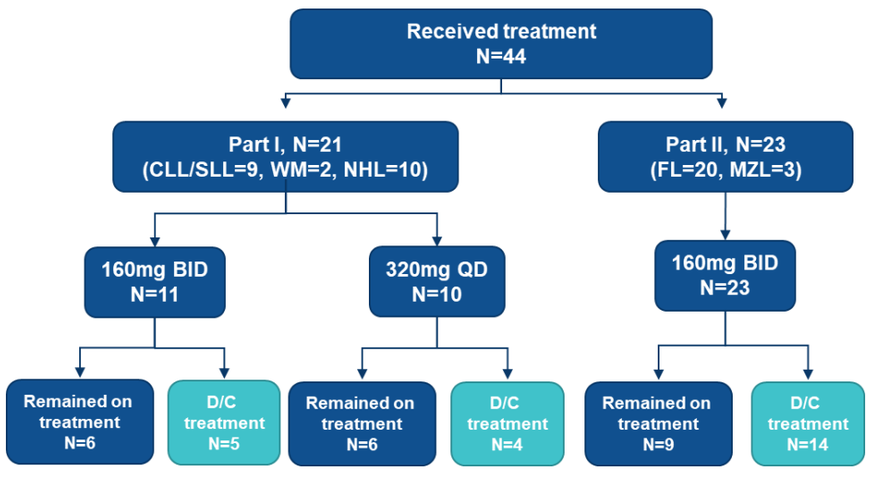
METHODS

- This study was designed to investigate the safety, tolerability, pharmacokinetic, pharmacodynamics and preliminary antitumor activity of zanubrutinib in Chinese patients with B-cell malignancies, and to determine the Recommended Phase 2 Dose (RP2D) that was proposed in phase 2 study in China
- The study was conducted in 2 parts: the first part was the safety assessment of doses (320mg QD or 160mg BID), and the second part was the dose expansion (use the recommended dose, 160mg BID). Adverse events (AE) were graded per CTCAE v4.03, responses per standard criteria according to histology

QD, once daily; BID, twice daily; FL, Follicular Lymphoma; MZL, Marginal Zone Lymphoma

RESULTS

- As of the data cutoff date on15 Jun 2018, 44 patients have been enrolled and received Zanubrutinib treatment. The median follow-up was 9.5 months overall, with 21.1 months for the Part I 160 mg BID cohort, 20.9 months for the Part I 320 mg QD cohort, and 7.7 months for the Part II cohort. The study is ongoing.



- Overall, pharmacokinetics and pharmacodynamics of zanubrutinib in Chinese patients was consistent with previous observations in non-Chinese patients (cross trials comparison reported in CSCO 2018).
- No dose limiting toxicity (DLT) occurred. No unexpected safety signal was identified in Safety evaluation period (part I).
- No (treatment emergent adverse event) TEAE leading to death were reported. There were no reports of major hemorrhage, atrial fibrillation/flutter, Grade 3 or higher hypertension, tumor lysis syndrome, or second primary malignancies.

Table 1. Overview of Adverse Events

	BGB-3111 160 mg BID (N = 34) n (%)	BGB-3111 320 mg QD (N = 10) n (%)	Total (N = 44) n (%)
Patients with at least one TEAE	33 (97.1)	10 (100.0)	43 (97.7)
Grade 3 or Higher	17 (50.0)	6 (60.0)	23 (52.3)
Serious	4 (11.8)	2 (20.0)	6 (13.6)
Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
Leading to Treatment Discontinuation	3 (8.8)	0 (0.0)	3 (6.8)
Leading to Dose Interruption	2 (5.9)	2 (20.0)	4 (9.1)

Table 2. Safety Summary (Common TEAE)

Preferred Term	BGB-3111 160 mg BID (N = 34) n (%)	BGB-3111 320 mg QD (N = 10) n (%)	Total (N = 44) n (%)
Patients with at least 1 TEAE	33 (97.1)	10 (100.0)	43 (97.7)
Neutrophil count decreased	15 (44.1)	7 (70.0)	22 (50.0)
Anemia	11 (32.4)	3 (30.0)	14 (31.8)
Upper respiratory tract infection	7 (20.6)	4 (40.0)	11 (25.0)
White blood cell count decreased	8 (23.5)	3 (30.0)	11 (25.0)
Platelet count decreased	8 (23.5)	2 (20.0)	10 (22.7)
Rash	7 (20.6)	3 (30.0)	10 (22.7)
Haematuria	6 (17.6)	3 (30.0)	9 (20.5)
Hyperuricaemia	6 (17.6)	3 (30.0)	9 (20.5)

Note: Incidence of TEAEs by Preferred Term in ≥ 20% of Total Patients

Table 3. Safety Summary (Grade ≥3 TEAE)

Preferred Term	CLL/SLL (N = 9) n (%)	MCL (N = 2) n (%)	WM (N = 2) n (%)	FL (N = 26) n (%)	MZL (N = 5) n (%)	Total (N = 44) n (%)
Patients with at least 1 Grade 3 or Higher TEAE	6 (66.7)	1 (50.0)	1 (50.0)	12 (46.2)	3 (60.0)	23 (52.3)
Neutrophil count decreased	5 (55.6)	1 (50.0)	1 (50.0)	3 (11.5)	1 (20.0)	11 (25.0)
Neutropenia	3 (33.3)	0 (0.0)	0 (0.0)	2 (7.7)	0 (0.0)	5 (11.4)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	2 (40.0)	4 (9.1)
White blood cell count increased	1 (11.1)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)	4 (9.1)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	2 (40.0)	3 (6.8)
Thrombocytopenia	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.8)	1 (20.0)	3 (6.8)

Incidence of Grade 3 or Higher TEAE by Preferred Term in ≥ 3 Patients

- Overall, 9 of 9 (100%) CLL/SLL patients, 1 of 2 (50%) WM patients, 1of 2 (50%) MCL patients, and 11 of 26 (42.3%) FL patients achieved a partial response or better.

Table 4. Efficacy Summary

Response Category	CLL/SLL (N = 9) n (%)	MCL (N = 2) n (%)	WM (N = 2) n (%)	FL (N = 26) n (%)	MZL (N = 5) n (%)	Total (N = 44) n (%)
Best Overall Response						
CR	2 (22.2)	1 (50.0)	0 (0.0)	2 (7.7)	0 (0.0)	5 (11.4)
CRi	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
VGPR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PR	6 (66.7)	0 (0.0)	1 (50.0)	9 (34.6)	0 (0.0)	16 (36.4)
PR-L	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)
MR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SD	0 (0.0)	1 (50.0)	1 (50.0)	8 (30.8)	3 (60.0)	13 (29.5)
PD	0 (0.0)	0 (0.0)	0 (0.0)	4 (15.4)	0 (0.0)	4 (9.1)
NE	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.5)	2 (40.0)	5 (11.4)
Overall Response Rate [1]	9 (100.0)	1 (50.0)	1 (50.0)	11 (42.3)	0 (0.0)	22 (50.0)
95% CI	(66.4, 100.0)	(1.3, 98.7)	(1.3, 98.7)	(23.4, 63.1)	(0.0, 52.2)	(34.6, 65.4)

Abbreviations: CR, complete response; CRi, complete response with incomplete bone marrow recovery; VGPR, very good partial response; PR, partial response; PR-L, partial response with lymphocytosis; MR, minor response; SD, stable disease; PD, progressive disease; NE, not estimable.
[1] Overall response includes best overall response being non-SD, non-PD and non-NE.

CONCLUSIONS

- Zanubrutinib was generally well tolerated in patients from China with B cell malignancies. The study also showed the preliminary antitumor activity. Currently, a number of Phase 2 and 3 clinical trials are being conducted globally including China, to further investigate the role of zanubrutinib in the treatment of B-cell malignancies.

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