A phase I clinical study to investigate the safety, tolerability and pharmacokinetics/ pharmacodynamics of BTK inhibitor BGB-3111 in Chinese patients with B-cell lymphoma

Yuqin Song[1], Junyuan Qi[2], Wei Xu[3], Dengju Li[4], Jianfeng Zhou[4], Jianyong Li[3], Lugui Qiu[2], Xiajun Xu[5], Haiyi Guo[5], Lai wang[5], Jane Huang[5], William Novotny[5],Shibao Feng[5], Jun Zhu[1]*

*Corresponding Author
1 Beijing Cancer Hospital (Peking University Cancer Hospital), Beijing, China; 2 Chinese Academy of Medical Sciences, Blood Diseases Hospital (Institute of Hematology), Tianjin, China; 3 Jiangsu Province Hospital, Nanjing, China; 4 Tongji Hospital, affiliated Huazhong University of Science and Technology, Wuhan, Hubei, China; 5 BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA

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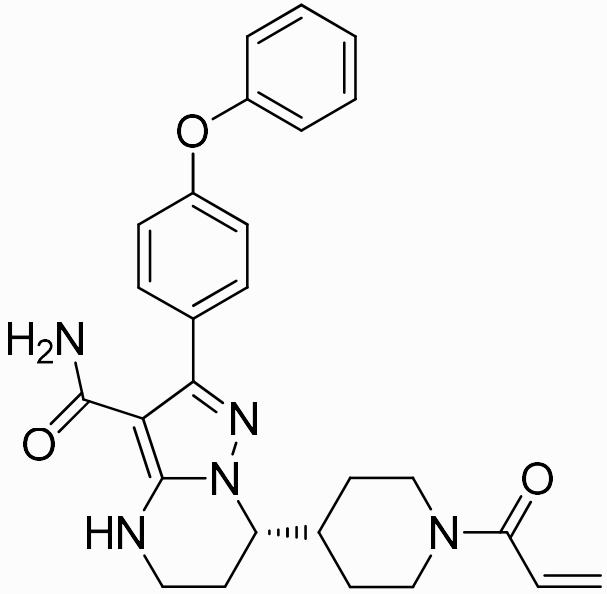
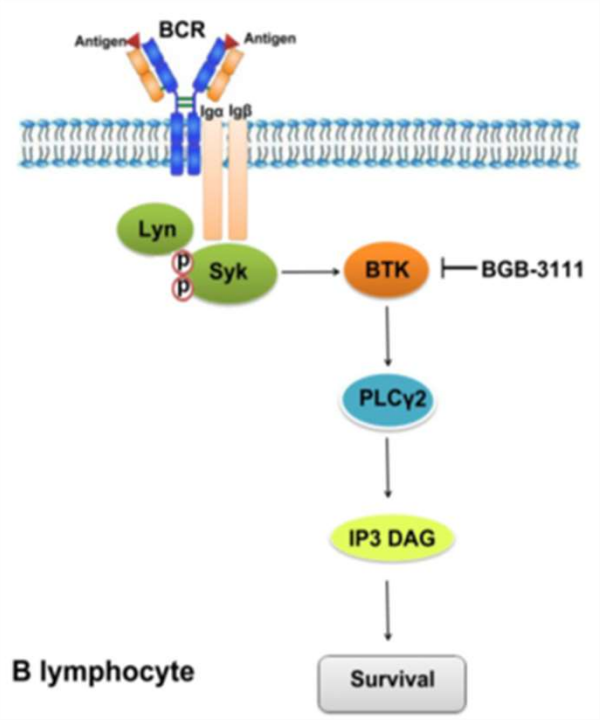
BGB-3111: Investigational Small Molecule Inhibitor of BTK

INN: Zanubrutinib

Code: BGB-3111





- Molecular Weight：471.55
- Molecular Formula：C27H29N5O3

- IC50：0.3 nM
- Based on preclinical studies, BGB-3111 is a potent, specific and irreversible BTK inhibitor
- Good pharmacokinetic properties, high oral availability with half-life in about 4 hours

BGB-3111: Higher selectivity

Targets	Assays	Ibrutinib IC_{50} (nM)	BGB-3111 IC_{50} (nM)	Ratio (BGB-3111:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	0.5
	Rec-1 Proliferation	0.34	0.36	1.1
	BTK Occupation Cellular Assay	2.3	2.2	1.0
	BTK Biochemical Assay	0.20	0.22	1.1
EGFR	p-EGFR HTRF Cellular Assay	101	606	6.0
	A431 Proliferation	323	3210	9.9
ITK	ITK Occupancy Cellular Assay	189	3265	17
	p-$PLC_{\gamma 1}$ Cellular Assay	77	3433	45
	IL-2 Production Cellular Assay	260	2536	9.8
	ITK Biochemical Assay	0.9	30	33
JAK3	JAK3 Biochemical Assay	3.9	200	51
HER2	HER2 Biochemical Assay	9.4	661	70
TEC	TEC Biochemical Assay	0.8	1.9	2.4

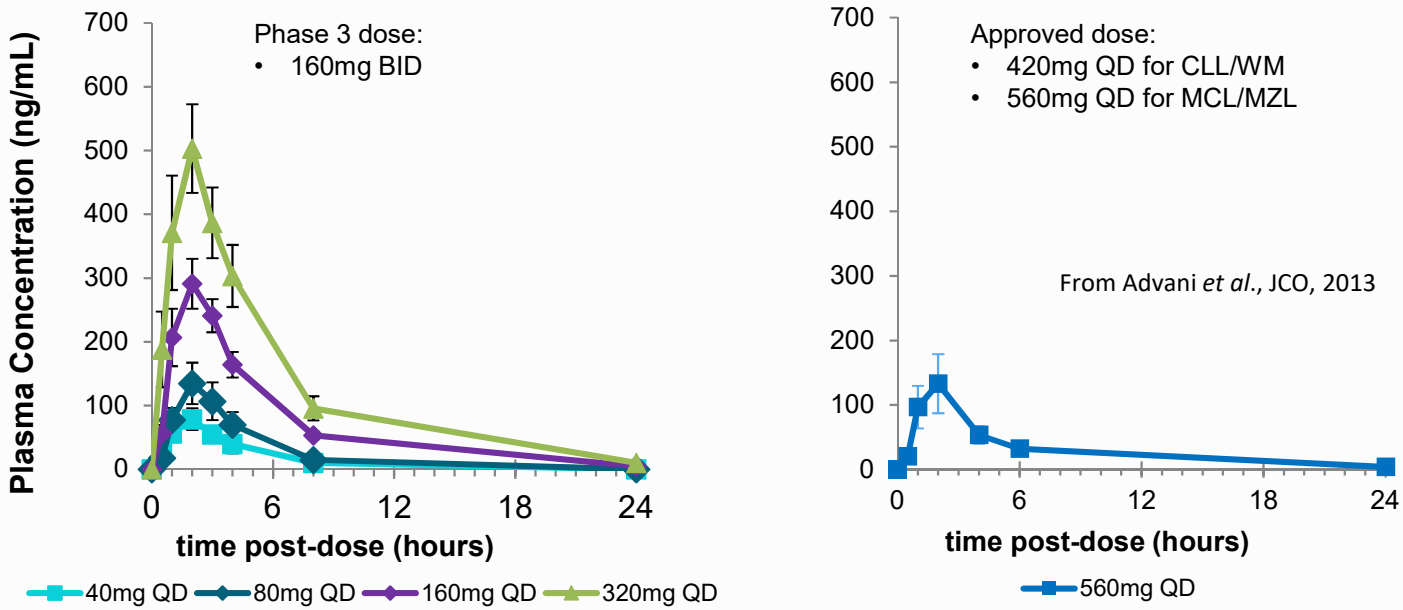
BTK=Bruton's tyrosine kinase, EGFR=epidermal growth factor receptor, HTRF=Homogeneous Time Resolved Fluorescence, IC_{50}=half maximal inhibitory concentration, ITK=interleukin-2-inducible T-cell kinase, JAK3=Janus kinase 3, HER2=human epidermal growth factor receptor 2, IL-2=interleukin-2, PLC=phospholipase C, REC-1=DNA repair exonuclease, TEC=non-receptor protein-tyrosine kinase

Tam CS. Blood. 2016;128:642.

BGB-3111: Pharmacokinetics

BGB-3111[1] | **Ibrutinib[2]**

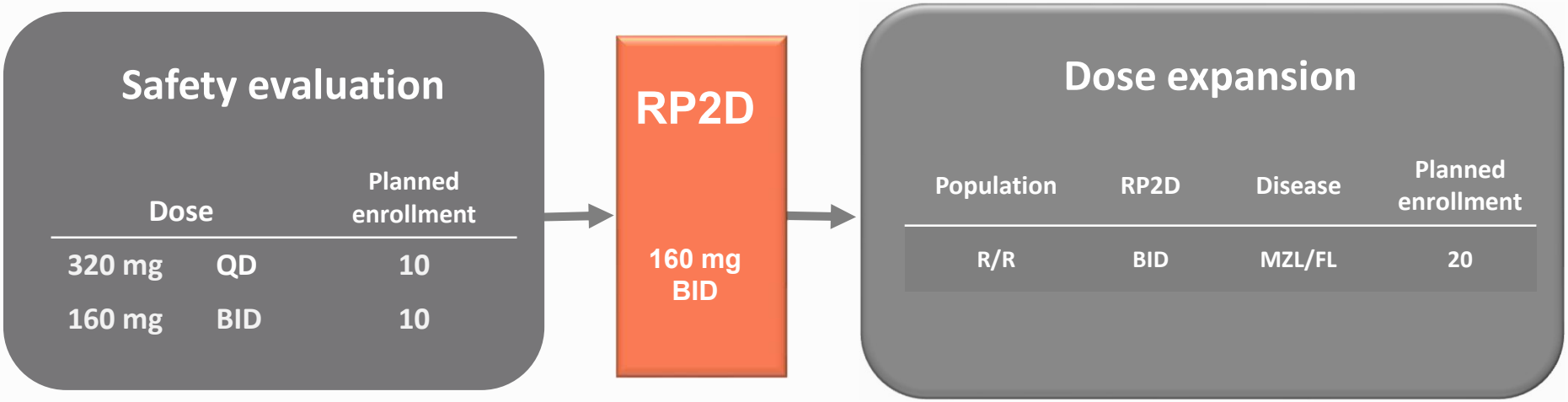
Data from respective phase 1 clinical trials



- C_{max} and AUC of BGB-3111 80mg QD equivalent to that of ibrutinib at 560 mg
- The free drug exposure of BGB-3111 at 40 mg QD was similar to that of ibrutinib at 560 mg.

1. Tam CS et al. Blood.2015;126:832 [oral presentation]. 2. Adapted from Advani RH et al. J Clin Oncol. 2013;31(1):88-94.

BGB-3111-1002: Phase 1 study in China

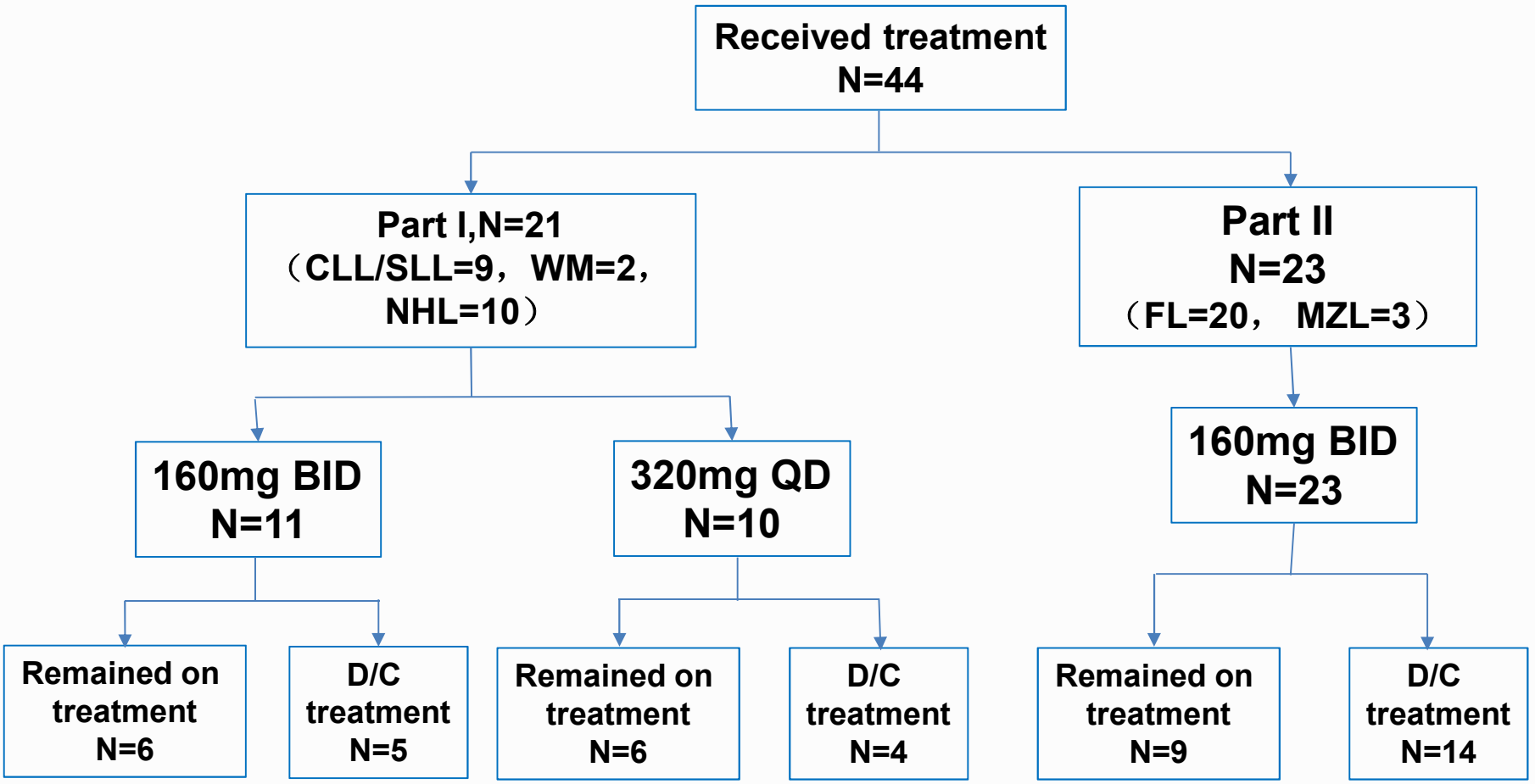


FL, Follicular Lymphoma; MZL, Marginal Zone Lymphoma

Inclusion Criteria:

- Diagnosis:
  - Safety evaluation：Refractory or relapsed B-cell lymphoma defined by WHO classification
  - Dose expansion：Refractory or relapsed follicular lymphoma (FL) and marginal zone lymphoma (MZL) defined by WHO classification
- ≥ 1 lines previous treatment
- ECOG 0-1
- Adequate hematological function, defined by neutrophils ≥ 1,000/μL, hemoglobin≥70 g/L and platelets ≥ 50,000/μL if bone marrow involved; or platelets ≥ 70,000/μL if no bone marrow involved.
- Without obvious cardiac diseases

BGB-3111-1002 Disposition of Patients



Note: NHL=non-hodgkin's lymphoma, not including CLL/SLL or WM,
Data cut off date was 15/Jun/2018

BGB-3111-1002: Demographics and Baseline Characteristics

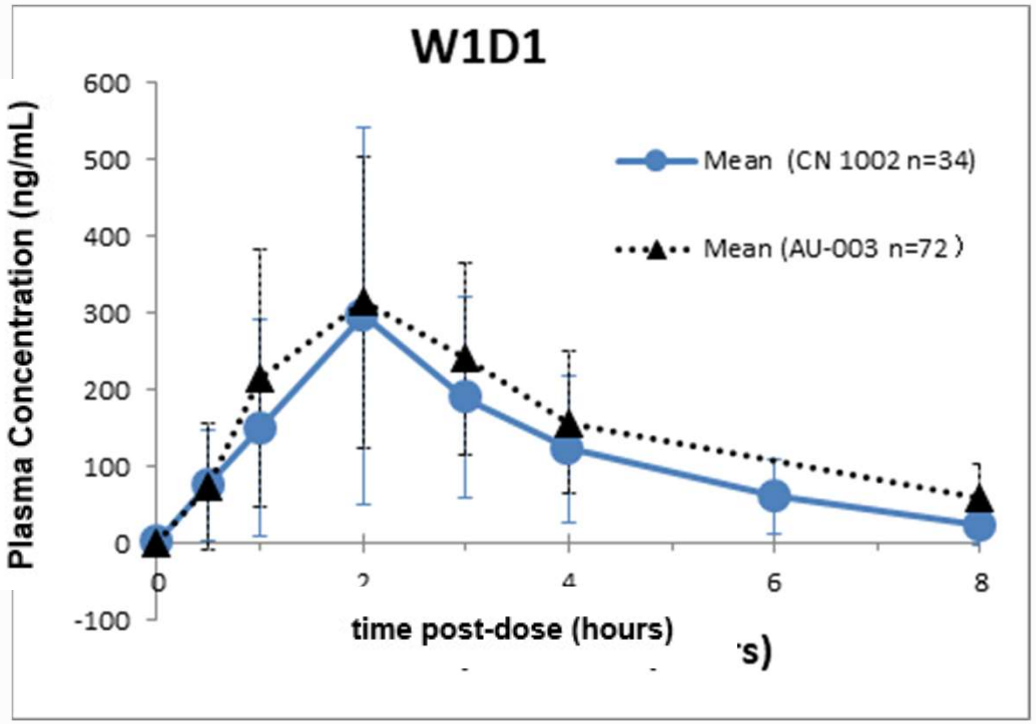
Parameter	Part I		Part II	Total N=44 n (%)
	160 mg BID N=11	320 mg QD N=10	160 mg BID N=23	
Age				
Mean (Standard Deviation)	51.9 (10.65)	52.1 (10.57)	48.4 (11.85)	50.1 (11.18)
Median	54.0	55.0	46.0	52.0
Age group, n(%)				
< 65 years	10 (90.9)	9 (90.0)	21 (91.3)	40 (90.9)
≥ 65 years	1 (9.1)	1 (10.0)	2 (8.7)	4 (9.1)
Gender, n(%)				
Male	9 (81.8)	7 (70.0)	8 (34.8)	24 (54.5)
Female	2 (18.2)	3 (30.0)	15 (65.2)	20 (45.5)
ECOG performance status, n (%)				
0	4 (36.4)	5 (50.0)	17 (73.9)	26 (59.1)
1	7 (63.6)	5 (50.0)	5 (21.7)	17 (38.6)
2	0 (0.0)	0 (0.0)	1 (4.3)	1 (2.3)
BMI (kg/m^2)				
Mean (Standard Deviation)	25.87 (2.788)	24.04 (4.004)	23.88 (3.249)	24.41 (3.360)
Median	25.80	22.24	24.57	24.59

BGB-3111-1002: Disease History and Baseline Characteristics

	Part I		Part II	
	160 mg BID (N = 11)	320 mg QD (N = 10)	160 mg BID (N = 23)	Total (N = 44)
Diagnosis, n (%)				
CLL	4 (36.4)	3 (30.0)	0 (0.0)	7 (15.9)
WM	1 (9.1)	1 (10.0)	0 (0.0)	2 (4.5)
Other NHL	6 (54.5)	6 (60.0)	23 (100.0)	35 (79.5)
Bone marrow biopsy infiltration of abnormal lymphocytes, n (%)				
Yes	5 (45.5)	6 (60.0)	9 (39.1)	20 (45.5)
No	6 (54.5)	4 (40.0)	14 (60.9)	24 (54.5)
B-lymphoid nodules, n (%)				
Diffused	3 (27.3)	2 (20.0)	5 (21.7)	10 (22.7)
Clustered	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not available	8 (72.7)	8 (80.0)	18 (78.3)	34 (77.3)
Constitutional symptoms, n (%)				
Weight Loss	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	0 (0.0)	0 (0.0)	1 (4.3)	1 (2.3)
Sweats	1 (9.1)	0 (0.0)	3 (13.0)	4 (9.1)

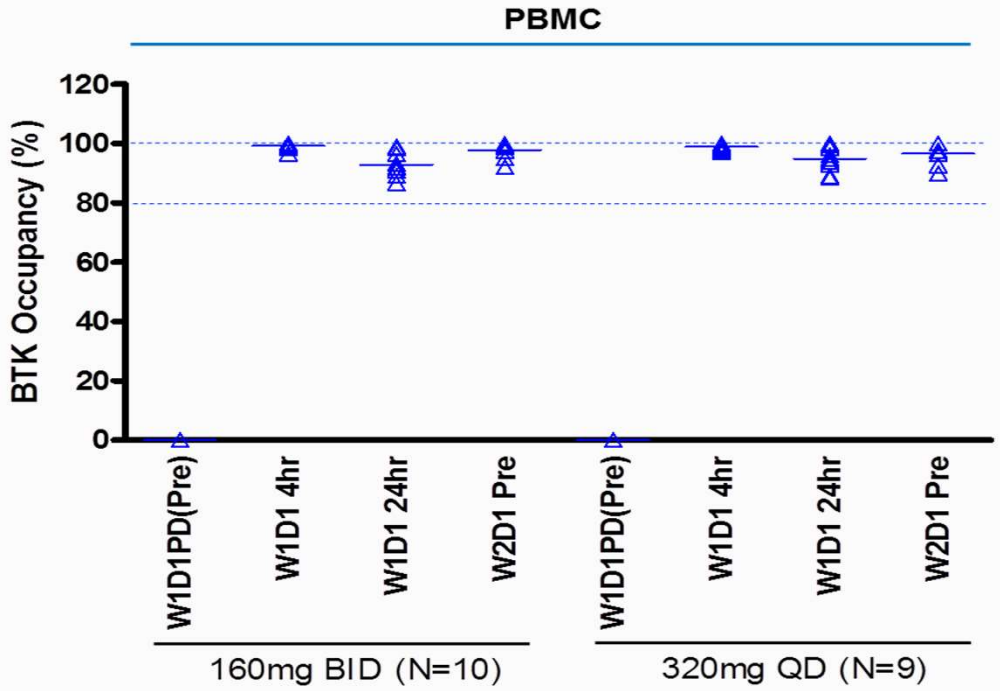
Pharmacokinetics Profile of BGB- 3111 in Chinese and non-Chinese Subjects

160 mg: AU-003 vs 1002* (Part I)



The preliminary results of pharmacokinetics in study BGB-3111-1002 and BGB-3111-AU-003 indicate there is *no significant* difference of pharmacokinetics profile between Chinese and non-Chinese subjects.

BGB-3111-1002：BTK Occupancy in PMBC



Complete or >80% and sustained BTK occupancy in PBMCs was achieved at trough in Chinese patients with both single- and multiple-dose administrations

BGB-3111-1002: Overview of Adverse Events

(As of June 15, 2018)

	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[1]	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)
Treatment-Related[2]	33 (97.1)	10 (100.0)	43 (97.7)
Treatment-Related Grade 3 or Higher[1]	17 (50.0)	6 (60.0)	23 (52.3)
Treatment-Related Serious	4 (11.8)	2 (20.0)	6 (13.6)
Treatment-Related Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-Related Leading to Treatment Discontinuation	3 (8.8)	0 (0.0)	3 (6.8)
Treatment-Related Leading to Dose Interruption	2 (5.9)	2 (20.0)	4 (9.1)

[1] Adverse event grades are evaluated based on NCI-CTCAE (version 4.03).
[2] Related, possibly related, probably related, unlikely related, and with missing relationship.

- *No DLT occurred. No unexpected safety signal was identified in Safety evaluation period (part I).*
- *No TEAEs leading to death were reported.*

BGB-3111-1002: Safety Summary

Incidence of TEAEs by Preferred Term in ≥ 20% of Total Patients
(Part I and Part II Combined, as of June 15, 2018)

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)
Anaemia	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)

BGB-3111-1002: Safety Summary

Incidence of Grade 3 or Higher TEAE by Preferred Term in ≥ 2 Patients
(Part I and Part II Combined, as of June 15, 2018)

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)
Hyperuricaemia	0 (0.0)	0 (0.0)	1 (50.0)	1 (3.8)	0 (0.0)	2 (4.5)
Lymphocyte count increased	1 (11.1)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	2 (4.5)
Platelet count decreased	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	1 (20.0)	2 (4.5)
Upper respiratory tract infection	1 (11.1)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)

BGB-3111-1002: Analysis of Disease Response

(Part I and Part II Combined, as of June 15, 2018)

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)

[1] Overall response includes best overall response being non-SD, non-PD and non-NE.

BGB-3111-1002: Conclusion

- No DLT occurred in Safety evaluation period (part I).
- No unexpected safety signal was identified. Zanubrutinib demonstrated a favorable safety and tolerability profile in Chinese patients with B cell malignancies.
- Preliminary results of a pharmacokinetics study demonstrated no significant difference in the pharmacokinetics profile between Chinese and non-Chinese subjects.
- Based on the safety, tolerability, pharmacokinetics and efficacy data, the recommended dosage,160 mg BID, was proposed in phase II study in China.