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UPDATED SAFETY AND EFFICACY DATA IN THE PHASE 1 TRIAL OF PATIENTS WITH MANTLE CELL LYMPHOMA (MCL) TREATED WITH BRUTON TYROSINE KINASE (BTK) INHIBITOR ZANUBRUTINIB (BGB-3111)

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Introduction: Zanubrutinib, an investigational BTK inhibitor, has demonstrated greater selectivity for BTK vs other TEC- and EGFR-family kinases in biochemical assays and shown favorable PK/PD properties in preclinical studies. In phase 1 testing, high plasma concentrations were achieved, resulting in complete and sustained 24-hour BTK inhibition in blood and lymph nodes in patients (pts) treated at 160 mg twice daily (bid; Tam. *Blood* 2016;128:642). Here, we present updated safety and efficacy data from pts with MCL.

Methods: This is a global, phase 1 study investigating zanubrutinib in pts with B-cell malignancies with indication-specific expansion cohorts. In the expansion phase, enrolled pts received zanubrutinib 320 mg daily or 160 mg bid (the RP2D). Treatment emergent adverse events (TEAEs) were summarized according to NCI CTCAE v4.03 and responses were assessed by CT scans as per Lugano Classification (Cheson. *J Clin Oncol* 2014;32:3059).

Results: As of 16 Sep 2018, 48 MCL pts were enrolled: 37 relapsed/refractory (R/R) and 11 treatment-naïve (TN) (**Table**). Of the 48 pts, 45 were evaluable for efficacy; 3 were not efficacy evaluable as they had not yet reached the first 12-week efficacy assessment. Median follow-up for efficacy evaluable pts was 16.0 mo (range, 1.6–38.2). Twenty-six pts discontinued treatment (16 due to progressive disease [PD]; 10 due to TEAEs including peripheral edema, small cell lung cancer, renal hematoma, ANCA-positive vasculitis with acute kidney injury, subdural hematoma, and myelodysplastic syndrome, pneumonia (2 pts), congestive cardiac failure, thalamic infarction). Five pts died due to TEAEs (1 pneumonia, 1 congestive cardiac failure, 1 thalamic infarction, and 2 sepsis/septic shock), none of which were assessed by investigator as related to zanubrutinib. Most common TEAEs of any cause (≥15% of pts) included diarrhea (35%), petechiae/purpura/contusion (31%), upper respiratory tract infection (27%), fatigue (25%), constipation (21%), rash (19%), back pain (17%), headache (17%) and peripheral edema (17%). Overall response rate (ORR) for TN, R/R and overall was 87.5% (7/8), 86.5% (32/37) and 86.7% (39/45) respectively (**Table**). Responses were based on computed tomography scans for most pts, as positron-emission tomography was not required. Median progression-free survival was 15.4 mo (**Table**).

Conclusions: Zanubrutinib monotherapy was shown to be well tolerated and highly active in pts with MCL, with high ORR and rate of CR.

Keywords: BTK inhibitors; mantle cell lymphoma (MCL).

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TABLE 1 Patient Characteristics, Safety, and Efficacy

Patient characteristics	**N = 48**		
Median (range) age, y	71 (42–90)		
ECOG PS, n (%)			
0	20 (41.7)		
1	22 (45.8)		
2	6 (12.5)		
Stage at study entry, n (%)			
Stage I	3 (6.3)		
Stage II	1 (2.1)		
Stage III	4 (8.3)		
Stage IV	40 (83.3)		
MIPI, n (%)			
Low risk	12 (25.0)		
Intermediate risk	18 (37.5)		
High risk	18 (37.5)		
Disease status, n (%)			
Treatment-naïve	11 (22.9)		
Relapsed/refractory	37 (77.1)		
Median (range) no. of prior therapies	1 (1–4)		
Median (range) follow-up, mo	15.1 (0.6–38.2)		
Bulky disease >10 cm, n (%)	3 (6.3)		
Safety, n (%)	**N = 48**		
Any AE	47 (97.9)		
Grade ≥3 AEs	28 (58.3)		
Serious AEs	19 (39.6)		
AEs leading to zanubrutinib discontinuation	11 (22.9)		
AEs leading to death	5 (10.4)		
Efficacy			
Best response per investigator (n)	**TN (n=8)**	**R/R (n=37)**	**Overall (n=45)**
Overall response rate, n (%); 95% CI	7 (87.5); 47.3, 99.7	32 (86.5); 71.2, 95.5	39 (86.7); 73.2, 94.9
Complete response, n (%)	3 (37.5)	11 (29.7)	14 (31.1)
Partial response, n (%)	4 (50.0)	21 (56.8)	25 (55.6)
Stable disease, n (%)	0 (0.0)	2 (5.4)	2 (4.4)
Progressive disease, n (%)	1 (12.5)	3 (8.1)	4 (8.9)
Median follow up (min, max)	8.6 (1.6, 25.0)	17.1 (1.9, 38.2)	16.0 (1.6, 38.2)
Duration of response (mo)	**R/R (n=32)**		**Overall (n=39)**
Follow up, median (min, max)[a]	14.7 (0.0, 28.2)	14.3 (0.0, 28.2)	
Median (95% CI)[b]	14.7 (10.6, 18.5)	14.7 (10.6, 18.5)	

Abbreviations: AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; CI, confidence interval.
[a]Follow-up time is estimated by the reverse Kaplan-Meier method.
[b]Median is estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.

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