Safety and activity of the highly specific BTK inhibitor, BGB-3111 plus obinutuzumab in patients (pts) with follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL)

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Introduction: BGB-3111 is a potent and irreversible Bruton tyrosine kinase (BTK) inhibitor, designed to minimize off target inhibition of other TEC- and EGFR-family kinases. BGB-3111 has significantly less inhibitory effect against ITK and does not inhibit ITK-mediated rituximab (R)-induced antibody-dependent cell-mediated cytotoxicity (ADCC). BGB-3111 has shown significant activity in a variety of B-cell malignancies, especially CLL/small lymphocytic leukemia (SLL) and Waldenström macroglobulinemia (*Blood* 2016;128:642; *Blood* 2016;128:1216). Obinutuzumab (O) is a second-generation anti-CD20 humanized monoclonal antibody that has increased ADCC activity vs R and is more effective than R when combined with chemotherapy in CLL/SLL and FL. Preliminary results of a phase 1b study of BGB-3111 plus O in pts with CLL/SLL and FL are presented.

Methods: This is an ongoing, open-label, multicenter, phase 1b study of the combination of BGB-3111 and O in pts with B-cell malignancies with indication-specific expansion cohorts. Reported here are interim safety and activity results for the CLL/SLL and FL cohorts.

Results: As of 15 Dec 2016, 40 pts with CLL/SLL (17 pts with treatment-naïve [TN]; 23 pts with relapsed/refractory [R/R]), and 13 pts with FL were enrolled. Demographic and disease characteristics are shown in Table 1. Median follow-up time was 4.1 months for CLL/SLL and 6.2 months for FL. BGB-3111 plus O was well tolerated. No fatal adverse events (AEs) occurred; only 1 AE led to treatment discontinuation (squamous cell carcinoma in a pt with prior squamous cell carcinoma). Serious AEs (SAEs) were reported in 25.0% of CLL/SLL pts and 23.1% of FL pts; there was only 1 SAE related to O (infusion-related reaction) and 1 SAE related to BGB-3111 (pneumonia). There were no AEs of atrial fibrillation. Pts were evaluable for response if they had completed baseline and ≥1 on-treatment response assessment. Objective response rates (complete response [CR] + partial response + partial response with lymphocytosis) were 88.9%, 86.7%, and 81.8% in TN CLL/SLL, R/R CLL/SLL, and R/R FL, respectively, with 3 CRs in R/R CLL/SLL and 5 CRs in FL. Two pts (1 R/R CLL;1 FL) experienced disease progression; no instances of disease transformation occurred.

Conclusions: BGB-3111 plus O is well tolerated and highly active in CLL/SLL and FL. Most notably, the response rate in FL appears to be higher than that reported with BTK inhibitors or anti-CD20 therapy alone.

	TN CLL/SLL (n=17)	R/R CLL/SLL (n=23)	R/R FL (n=13)
Demographics			
Median (range) age, y	68 (38-82)	68 (51-82)	56 (42-86)
Median no. of prior therapies (range)	0	1 (1-4)	1.5 (1-5)
Safety, n (%)			
Grade ≥3 AE	2 (11.8)	8 (34.8)	3 (23.1)
Serious AE	2 (11.8)	8 (34.8)	3 (23.1)
AEs leading to Rx discontinuation	0	1 (4.3)	0
Fatal AE	0	0	0
Efficacy (Evaluable), Best Response	**n=9**	**n=15**	**n=11**
Median follow-up, mo	2.8	4.7	6.2
CR, n/N (%)	0	3/15 (20.0)	5/11 (45.5)
PR, n/N (%)	8/9 (88.9)	10/15 (66.7)	4/11 (36.4)
SD, n/N (%)	1/9 (11.1)	1/15 (6.7)	1/11 (9.1)
PD, n/N (%)	0	1/15 (6.7)	1/11 (9.1)