Safety and Activity of the Highly Specific BTK Inhibitor BGB-3111 in Patients with Indolent and Aggressive Non Hodgkin's Lymphoma

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Introduction

Bruton's Tyrosine Kinase (BTK) plays a critical role in B-cell receptor (BCR) signaling, which mediates B-cell proliferation, migration, and adhesion (Rickert, 2013; Aalipour, 2013; Choe, 2016). The BCR pathway is an established therapeutic target in multiple subtypes of non-Hodgkin's lymphoma (NHL). BGB-3111 is a potent, highly specific, and irreversible BTK inhibitor, with greater selectivity for BTK vs other TEC- and EGFR-family kinases and demonstrates favorable pharmacokinetic and pharmacodynamic properties. We have previously shown complete and sustained BTK occupancy in both peripheral blood mononuclear cells (PBMCs) and lymph nodes (LN) in patients (pts) treated at the 160 mg BID dose in a phase 1 trial (Tam et al. ASH 2016). A recent update of clinical data suggests that complete and sustained BTK occupancy is associated with durable responses in pts with CLL/SLL and Waldenström's macroglobulinemia (Seymour et al. ICML 2017; Trotman et al. ICML 2017). Here, we present early safety and efficacy data in pts with other NHL subtypes: relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), and marginal zone lymphoma (MZL).

Methods

This is an open-label, multicenter, phase 1b study of BGB-3111 in pts with B-cell malignancies. Dose escalation included pts with R/R B-cell malignancies, while the expansion phase enrolled disease-specific cohorts at the recommended phase 2 dose (320 mg/d, given once daily [QD] or split as 160 mg twice-daily [BID]). Response was assessed per ICML criteria (Cheson 2014).

Results

As of 18 May 2017, 75 pts with NHL were enrolled, including 23 DLBCL, 31 MCL, 14 FL, and 7 MZL pts. Patient characteristics are shown in the Table. With the exception of 1 pt with treatment-naive MCL, all pts had R/R disease.

Safety: Median follow-up was 7 months (range, 0.3-31.9). The most frequent adverse events (AEs) of any cause were contusion (22.7%), upper respiratory tract infection (21.3%), diarrhea (18.7%), constipation (17.3%), thrombocytopenia, cough, fatigue (16%), anemia (14.7%), neutropenia, dyspnea, nausea, pruritus (13.3%), pyrexia (12%), rash (10.7%), and back pain (9.3%). No cases of atrial fibrillation have been reported. The most frequently reported ≥ Grade 3 AEs of any cause were neutropenia (10.7%), anemia (9.3%), thrombocytopenia (8%), and pneumonia (6.7%). One Grade 3 renal hematoma and one Grade 3 GI hemorrhage were reported. Twenty-eight pts experienced at least one serious AE: of those, 4 were considered related to BGB-3111, including (all n=1) pneumonia, urinary tract infection, diarrhea, and pneumonitis. Seven pts discontinued BGB-3111 due to an AE (n=1 each): acute kidney injury, myelodysplastic syndrome, worsening diarrhea, one patient for renal hematoma and cognitive disorder, as well as 3 fatal AEs designated by the investigator as unrelated to BGB-3111 including pneumonia, cardiac failure, and septic shock. Additional unrelated fatal events included (n=1 each) multi-organ failure secondary due to disease progression, abdominal pain secondary due to disease progression, and death of unknown etiology.

Activity: Of the 62 NHL pts evaluable for response (> 12 weeks follow-up or discontinuation before 12 weeks), the objective response rate was 58.1% (36/62) overall, 60.9% (28/46) in the aggressive lymphoma (AL) group, and 50.0% (8/16) in the indolent lymphoma group (IL). Most responses were partial responses: 45.2% (28/62) overall, 45.7% (21/46) in AL, and 43.8% (7/16) in IL. Stable disease was seen in 13/62 (21.0%). Nine pts progressed by the first response assessment (all DLBCL pts), and 4 AL discontinued before assessment. Activity is summarized in the Table, with percentage change in lymph nodes shown in the Figure.

Reasons for discontinuing BGB-3111 included 32 pts for progression, 7 for AE, 3 for withdrawal of consent, and 3 for other.

Conclusions

BGB-3111 is well tolerated and active as a monotherapy in multiple NHL subtypes. Evaluation of BGB-3111 in NHL, both as monotherapy as well as in combination with other agents, is continuing in Phase 2 trials.

Table. Demographics, Safety, and Efficacy of Patients Treated with BGB-3111

	Aggressive lymphoma (DLBCL, MCL)	Indolent lymphoma (FL, MZL)	Overall
	(N=54)	(N=21)	(N=75)
Demographics			
Median (range) age, y	70 (42-86)	63.5 (41-79)	68 (41-86)
ECOG PS, N (%)			
0	21 (38.9)	11 (52.4)	32 (42.7)
1	27 (50)	9 (42.9)	36 (48.0)
2	6 (11.1)	1 (4.8)	7 (9.3)
Median no. of prior therapies (range)	2 (0-10)	2 (1-8)	2 (0-10)
Median mo follow-up (range)	5.1 (0.5-31.9)	10.2 (0.3-18.4)	7 (0.3-31.9)
Prior Rx, N (%)			
Naïve	1 (1.9)	0	1 (1.3)
R/R	53 (98.1)	21 (100)	74 (98.7)
Bulky Disease (lesion > 10cm), N (%)	3 (5.6)	0	3 (4.0)
Safety, N (%)			
Any AE	51 (94.4)	21 (100)	72 (96)
Grade ≥3 AE	32 (59.3)	6 (28.6)	38 (50.7)
Serious AE related	2 (3.7)	2 (9.5)	4 (5.3)
AEs leading to Rx discontinuation	6 (11.1)	1 (4.8)	7 (9.3)
Fatal AE	5 (9.3)	1 (4.8)	6 (8)
Efficacy (best response), N (%)	(N=46)	(N=16)	(N=62)
ORR	28 (60.9)	8 (50)	36 (58.1)
CR	7 (15.2)	1 (6.3)	8 (12.9)
PR	21 (45.7)	7 (43.8)	28 (45.2)
SD	5 (10.9)	8 (50)	13 (21.0)
PD	9 (19.6)	0	9 (14.5)
Not evaluable	4 (8.7)	0	4 (6.5)

AE, treatment-emergent adverse event; ECOG PS, Eastern Cooperative Group Performance Status; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; Rx, treatment; SD, stable disease; TN, treatment-naïve; DLBCL, diffuse large-B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; AL, aggressive lymphoma; IL, indolent lymphoma. "not evaluable" means pt left study for reason other than PD before first response assessment. Note: most responses assessed with CT scan, but some used PET-CT.

Figure. Best Percent Change in SPD