Safety and Activity of the Highly Specific BTK Inhibitor BGB-3111 in Combination with the PD-1 inhibitor BGB-A317 in Patients with B-cell lymphoid malignancies

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Introduction

BGB-3111 is a potent, highly specific, and irreversible Bruton tyrosine kinase (BTK) inhibitor, with greater selectivity for BTK vs other TEC- and EGFR-family kinases, and demonstrates favorable pharmacokinetic and pharmacodynamics properties (Tam et al. ASH 2016). BGB-A317, a humanized IgG4 variant monoclonal antibody with no Fc gamma receptor binding, targets the programmed cell death-1 (PD-1) receptor and is being developed for the treatment of solid and hematologic malignancies (Friedlander, ASCO, 2017). The combination of PD-1/PD-L1 inhibitors with BCR pathway inhibitors is being evaluated in different B-cell malignancies with the expectation of greater benefit for patients. Here, we present early safety data from a Phase 1b trial exploring the combination of BGB-3111 and BGB-A317.

Methods

This is an open-label, multicenter, phase 1b study to evaluate safety, tolerability, and preliminary efficacy of BGB-3111 in combination with BGB-A317 in subjects with B-cell malignancies, including Waldenström's macroglobulinemia (WM), aggressive and indolent non-Hodgkin's lymphoma, and transformed CLL/FL amongst other B-cell malignancies. The study includes a standard 3+3 dose escalation phase followed by dose expansion. The dose levels are: Cohort 1, BGB-3111 320 mg once a day (QD) combined with BGB-A317 2.0 mg/kg every 3 weeks (Q3W); Cohort 2, BGB-3111 320 mg QD combined with BGB-A317 5.0 mg/kg Q3W; and Cohort 3, BGB-3111 160 mg BID combined with BGB-A317 200 mg (flat dose) Q3W.

Results

As of 01 June 2017, 25 pts were enrolled in the dose escalation portion of the trial: 15 pts in Cohort 1 and 10 pts in Cohort 2. Key patient characteristics, safety, and efficacy are shown in Table 1.

Safety: Median follow-up was 2.8 (range, 0.4-10.7) months. There were no dose-limiting toxicities (DLTs) in Cohort 1. Cohort 2 saw hemolysis in 2 pts, both with WM; one qualified as a DLT. These events were not associated with a positive direct antiglobulin test and resolved with immunosuppressive therapy, but resulted in the decision to exclude further enrollment of WM pts in the trial. No further DLTs were observed after exclusion of WM pts.

The most frequent AEs of any cause in Cohort 1 were diarrhea (n=4, 26.7%), fatigue (n=4, 26.7%), and pyrexia (n=3, 20%) and in Cohort 2 were contusion (n=3, 30%), anemia, hemolysis,

headache, peripheral edema, thrombocytopenia, and upper respiratory tract infection (n=2, 20% each). Frequent AEs ≥ Grade 3 from both Cohorts included anemia (n=32, 12%), and thrombocytopenia and hemolytic transfusion reaction (n=2, 8% each).

Serious AEs related to study treatment were seen in 8 patients: hemolysis (n=2), pneumonitis, infusion-related reaction, abscess limb, pneumonia, anemia, ulcerative keratitis, catheter site hemorrhage, autoimmune encephalitis, dyspnea, and eczema (n=1 each). The encephalitis could not be attributed to other causes and resolved with immunosuppressive therapy. No serious hemorrhages or atrial fibrillation have been reported to date.

Discontinuation due to adverse events occurred in six patients for the following AEs: hemolysis (n=2), nausea, lymph gland infection, ALT increased and GGT increased (same patient), auto-immune encephalitis, and progression-related complications (n=1 each).

Efficacy: Efficacy data is very early with limited follow-up and most pts treated at the lowest dose. So far, 30% of pts have responded, including responses in both WM pts as well as CRs seen in FL and non-GCB DLBCL pts.

Conclusions

The combination of BGB-3111 and BGB-A317 has a manageable toxicity profile in a wide variety of B-cell malignancies. Autoimmune adverse events, consistent with anti-PD-1 therapy, were observed and managed with supportive care. Notably, hemolysis in 2 WM patients suggest limitations of this combination in indolent lymphoid diseases such as WM, especially given the risk/ benefit profile of single-agent BGB-3111 in indolent settings.

Enrollment is now open for Cohort 3, which will be followed by expansion cohorts to further characterize safety and efficacy of the combination.

Table. Demographics, Safety, and Efficacy for Patients Receiving BGB-3111 in Combination With BGB-A317

	CLL	MCL	All DLBCL	FL, MZL, & WM	Transformed (Richter's & Transformed FL)	All Pts		
	Cohorts 1 & 2	Cohort 2	Cohorts 1 & 2	Cohorts 1 & 2	Cohorts 1 & 2	Cohort 1	Cohort 2	Cohorts 1 & 2
	(N=5)	(N=2)	(N=5)	(N=8)	(N=5)	(N=15)	(N=10)	(N=25)
Demographics								
Median (range) age, y	66 (47-76)	63 (62-64)	62 (27-65)	60.5 (55-71)	64 (51-71)	62 (27-76)	62.5 (47-68)	62 (27-76)
ECOG PS, N (%)								
0	2 (40)	1 (50)	1 (20)	5 (62.5)	1 (20)	6 (40)	4 (40)	10 (40)
1	0	0	3 (60)	3 (37.5)	4 (80)	7 (46.7)	3 (30)	10 (40)
2	3 (60)	0	1 (20)	0	0	2 (13.3)	2 (20)	4 (16)
3	0	1 (50)	0	0	0	0	1 (10)	1 (4)
Median no. of prior therapies (range)	5 (1-6)	2 (1-3)	4 (2-6)	3 (1-6)	5 (3-6)	5 (1-6)	2.5 (1-6)	4 (1-6)
Median mo follow-up (range)	1.7 (1.6-3.1)	2.8 (0.4-5.3)	2.8 (1.1-8.5)	4.6 (1.6-10.6)	6.7 (0.8-10.7)	2.8 (0.8-10.7)	3 (0.4-7.9)	2.8 (0.4-10.7)
Safety, N (%)								
Any AE	5 (100)	1 (50)	5 (100)	7 (87.5)	5 (100)	15 (100)	8 (80)	23 (92)
Grade ≥3 AE	3 (60)	1 (50)	3 (60)	4 (50)	4 (80)	8 (53.3)	7 (70)	15 (60)
Serious AE	1 (20)	1 (50)	5 (100)	3 (37.5)	3 (60)	7 (46.7)	6 (60)	13 (52)
AEs leading to Rx discontinuation	1 (20)	0	1 (20)	3 (37.5)	1 (20)	3 (20)	3 (30)	6 (24)
Fatal AE	0	0	1 (20)	0	0	0	1 (10)	1 (4.0)
Efficacy (best response), N (%)	(N=2)	(N=2)	(N=5)	(N=6)	(N=5)	(N=12)	(N=8)	(N=20)
ORR	0	0	1 (20)	3 (50)	2 (40)	3 (25)	3 (37.5)	6 (30)
CR	0	0	1 (20)	1 (16.7)	0	2 (16.7)	0	2 (10)
VGPR	–	–	–	1	–	–	1	1
PR	0	0	0	0	2 (40)	1 (8.3)	1 (12.5)	2 (10)
MR	–	–	–	1	–	–	1	1
SD	0	1 (50)	2 (40)	2 (33.3)	1 (20)	4 (33.3)	2 (25)	6 (30)
PD	1 (50)	1 (50)	2 (40)	0	2 (40)	4 (33.3)	2 (25)	6 (30)
Not evaluable	1 (50)	0	0	1 (16.7)	0	1 (8.3)	1 (12.5)	2 (10)

AE, treatment-emergent adverse event; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; Rx, treatment; SD, stable disease; ECOG PS, Eastern Cooperative Oncology Group Performance Status; RR, response rate; VGPR, very good partial response