Bruton's tyrosine kinase (BTK) inhibitor BGB-3111 demonstrates high very good partial response (VGPR) rate in patients with Waldenström macroglobulinemia (WM)

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Introduction: BTK inhibitors have been shown to be highly active in WM, particularly WM harboring a *MYD88* mutation (*MYD88*^{MUT}). BGB-3111 is a potent, specific, and irreversible BTK inhibitor. In primary patient (pt) samples, BGB-3111 demonstrated profound BTK inhibition with minimal inhibition of off-target kinases such as EGFR, ITK, JAK3, HER2, and TEC. In phase 1 testing, high plasma concentrations were safely achieved, resulting in complete, sustained BTK inhibition in blood and lymph nodes.

Methods: This was an open-label, multicenter, dose-finding phase 1 study of BGB-3111 in pts with B-cell malignancies, with indication-specific expansion cohorts. Here, updated safety and efficacy in WM are reported.

Results: As of 31 Dec 2016, 46 pts with WM were enrolled: median 2 prior therapies (range 0-8), median follow-up 8.2 months (1.4-28), 46 evaluable for safety, 41 for efficacy; 5 non-evaluable pts had either baseline IgM <500 mg/dL (n=3) recent plasmapheresis (n=1) or <12 weeks' follow-up (n=1). The most frequent adverse events (≥20%, all grade [Gr] 1 or 2) were upper respiratory infection (33%), contusion (28%), and constipation (22%). There were 3 treatment-related serious adverse events (Gr 2 atrial fibrillation [AF], Gr 2 headache, Gr 3 cryptococcal meningitis); in all 3 cases, BGB-3111 was withheld and safely resumed. 3 pts developed AF (one Gr 1, two Gr 2), and 1 developed Gr 3 diarrhea. No serious hemorrhage was reported. The objective response rate was 93% (38/41), with a major response rate of 78% (32/41): VGPR in 39% (16/41) and PR in 39% (16/41). Median time to response was 28 days. Response by *MYD88* and *CXCR4* mutational status, in pts with known status (n=32) is shown in Table 1. In pts with hemoglobin <10 g/dL at baseline, hemoglobin increased from a median of 8.8 g/dL (7.1-9.8) to

13.8 g/dL (10.7-16.1). IgM decreased from a median of 32.5 g/L (6-88.5) at baseline to 5.4 g/L (0.4-47.8).16 pts with baseline lymphadenopathy had a median reduction in SPD of 38% (9-81%). 2 pts (both in VGPR) have discontinued BGB-3111 for exacerbation of pre-existing bronchiectasis and prostate adenocarcinoma. The sole pt with disease progression remains on BGB-3111 with ongoing clinical benefit.

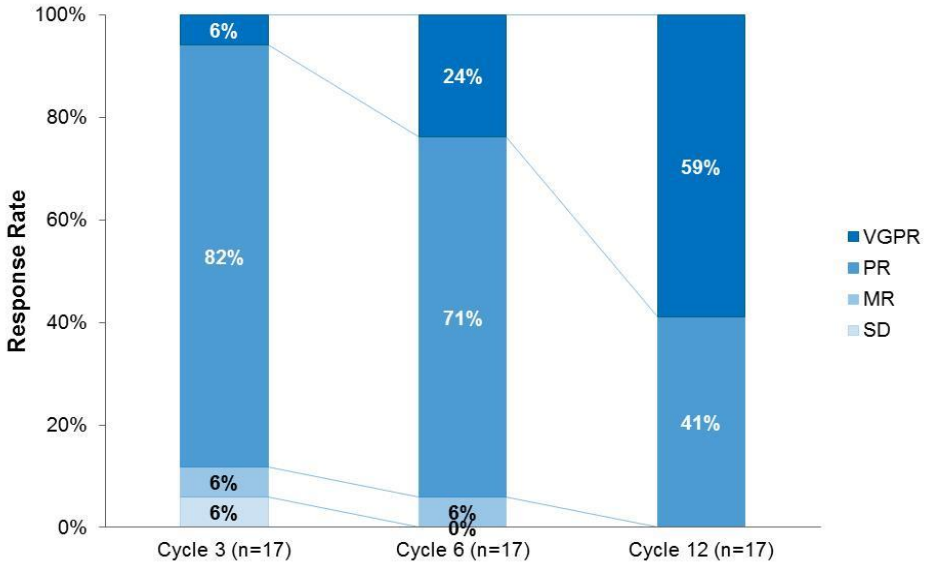
Conclusions: BGB-3111 is well tolerated and highly active in WM. Response depth, especially VGPR rate, and durability appear favorable. A phase 3 study comparing BGB-3111 with ibrutinib in WM is ongoing.

Table 1. Best response by follow-up time and mutational status

Best response by *MYD88/CXCR4* mutational status				
	Best response (N=32)	*MYD88^{L265P}/CXCR4^{WT}* (N=24)	*MYD88^{L265P}/CXCR4^{MUT}* (N=3)	*MYD88^{WT}/CXCR4^{WT}* (N=5)
VGPR	11 (34%)	10 (42%)		1 (20%)
PR	12 (38%)	9 (38%)	2 (67%)	1 (20%)
MR	7 (22%)	4 (17%)	1 (33%)	2 (40%)
SD	2 (6.2%)	1 (4.2%)		1 (20%)
Best response by duration of follow up				
	Best response (N=41)	>12 weeks of f/u (N=41)	>24 weeks of f/u (N=28)	>1 yr of f/u (N=17)
VGPR	**16 (39%)**	**2 (4.9%)**	**4 (14%)**	**10 (59%)**
PR	16 (39%)	25 (61%)	17 (61%)	7 (41%)
MR	6 (14%)	10 (24%)	5 (18%)	0 (0%)
SD	3 (7.3%)	4 (9.8%)	2 (7.1%)	0 (0%)
PD	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
ORR	**93%**	**90%**	**93%**	**100%**
MRR	**78%**	**66%**	**75%**	**100%**

f/u, follow-up; MR, minor response; MRR, major response rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

Figure 1. Improving depth of response for 17 pts with >1 year of f/u


100%
80%
60%
40%
20%
0%
Response Rate
6%
82%
6%
6%
24%
71%
6%
0%
59%
41%
Cycle 3 (n=17)
Cycle 6 (n=17)
Cycle 12 (n=17)
VGPR
PR
MR
SD