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Abstract #24

The BTK Inhibitor, BGB-3111, is Tolerable and Highly Active in Patients with Waldenström Macroglobulinemia: Interim Data From an Ongoing Phase 1 First-in-Human Trial

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Background

- Constitutively activated BTK, driven by MYD88L265P, is critical for tumor cell survival in WM[1]
- Ibrutinib, the first generation BTK inhibitor, is highly active in WM:
  - Major response rate 73% (including 16% VGPR)[2]
  - 68% 3-year event-free survival[3]
- BGB-3111 is a highly selective covalent, irreversible inhibitor of BTK with high oral bioavailability and exposure levels *in vivo*
- Presented here are interim results of BGB-3111 treatment of patients with WM from an ongoing Phase 1 trial of BGB-3111 in patients with B cell malignancies

[1]Yang et al. *Blood.* 2013.
[2] Treon et al. *NEJM.* 2015.
[3] Palomba et al. *IWWM.* 2016.

Table 1. BGB-3111: Kinase Selectivity Relative to Ibrutinib

Targets	Assays	Ibrutinib IC_{50} (nM)	BGB-3111 IC_{50} (nM)	Ratio (BGB-3111:Ibrutinib)
BTK	BTK-pY223 Cellular Assay	3.5	1.8	**0.5**
	Rec-1 Proliferation	0.34	0.36	**1.1**
	BTK Occupation Cellular Assay	2.3	2.2	**1.0**
	BTK Biochemical Assay	0.20	0.22	**1.1**
EGFR	p-EGFR HTRF Cellular Assay	101	606	**6.0**
	A431 Proliferation	323	3,210	**9.9**
ITK	ITK Occupancy Cellular Assay	189	3,265	**17**
	p-$PLC_{\gamma1}$ Cellular Assay	77	3,433	**45**
	IL-2 Production Cellular Assay	260	2,536	**9.8**
	ITK Biochemical Assay	0.9	30	**33**
JAK3	JAK3 Biochemical Assay	3.9	200	**51**
HER2	HER2 Biochemical Assay	9.4	661	**70**
TEC	TEC Biochemical Assay	0.8	1.9	**2.4**

Equipotent against BTK compared to ibrutinib. Higher selectivity vs EGFR, ITK, JAK3, HER2, & TEC.

Methods

Figure 1. BGB-3111: First-in-Human Study.

Part 1

Dose Escalation → RP2D

Cohort	Dose	n	# WM Patients
1	40 mg QD	4	2
2	80 mg QD	5	2
3	160 mg QD	6	1
4a	320 mg QD	6	1
4b	160 mg BID	4	0

Eligibility:

- WHO defined B-cell malignancy
- No available higher priority treatment
- ECOG 0-2
- ANC>1,000/ul, plts>100,000/ul*
- Adequate renal and hepatic function
- No significant cardiac disease†

* Growth factor/transfusion allowed.
† Anti-coagulation allowed.

Part 2a (paired LN biopsy):
- QD, 20 R/R MCL, MZL, FL, GCB DLBCL
- BID, 20 R/R MCL, MZL, FL, GCB DLBCL

Part 2b:
- BID, R/R non-GCB DLBCL, n=20

Part 2c:
- BID, R/R CLL/SLL, n=20

Part 2d:
- **BID, R/R WM, n=20**

Part 2e:
- QD, R/R CLL/SLL, n=20

Part 2f:
- **QD, TN & R/R WM, n=20**

Part 2g:
- QD, R/R MCL, n=20

Part 2h:
- QD, TN CLL/SLL, n=20

Part 2i:
- QD, TN MCL, n=20

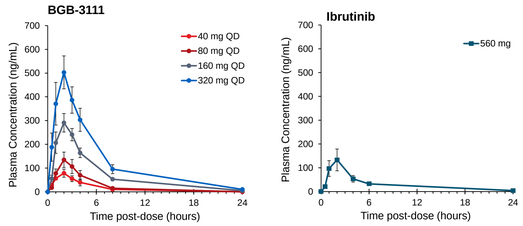
Conflict of Interest Disclosure:

1. **C. Tam:** Honoraria and Membership on an entity's Board of Directors or advisory committees (Roche, AbbVie); Honoraria and Research Funding (Janssen).
2. **S. Opat:** Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research funding, and Speakers Bureau (Roche): Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees and Research funding (Celgene); Consultancy, Honoraria , Membership on an entity's Board of Directors or advisory committees, Janssen: Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding and Speakers Bureau (Gilead); Honoraria and Membership on an entity's Board of Directors or advisory committees and Research funding (Takeda).
3. **G. Cull, J Trotman, P Marlton, M Ku, D, Ritchie, S. Ratnasingam, B., Augustson:** No conflicts to disclose.
4. **D. Gottlieb:** Membership on an entity's Board of Directors or advisory committees (Abbvie, Indee): Research Funding (Celgene).
5. **D. Simpson:** Research Funding (Amgen); Honoraria (Celgene, Roche, Janssen).
6. **M. A. Anderson:** Walter and Eliza Hall Institute of Medical Research receives milestone payments for the development of venetoclax (Walter and Eliza Hall Institute of Medical Research).
7. **M. Kirschbaum, L Wang, L Xue, E Hedrick:** Employment (BeiGene).
8. **J. Seymour:** Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding and Speakers Bureau (Abbvie, Janssen); Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees and Research Funding (Genentech); Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees and Speakers Bureau (Roche, Celgene, Gilead), Honoraria and Membership on an entity's Board of Directors or advisory committees (Takeda).
9. **A. Roberts:** Research Funding (Abbvie, Genetech).

Results

- Plasma exposure comparison for BGB-3111 *&* ibrutinib (Figure 2):
  - C_{max} and AUC of BGB-3111 at 80 mg is similar to those of ibrutinib at 560 mg
  - Free drug exposure of BGB-3111 at 40 mg is comparable to that of ibrutinib at 560 mg

Figure 2. Plasma exposure comparison.



Tam, et al., ASH, 2015. Adapted from Advani, et al., *JCO.* 2013.

- Complete and sustained BTK occupancy in PBMC & lymph node:
  - PBMC (Figure 3):
    - Complete BTK occupancy at the starting dose (40 mg)
  - Lymph node (Figure 4):
    - Paired lymph node biopsies were collected during screening or pre-dose on day 3
    - Median trough occupancy: 100% (160 mg BID) vs 94% (320 mg QD), p=0.002
    - Proportion >90% trough occupancy: 94% (160 mg BID) vs 58% (320 mg QD), p=0.027

Figure 3. PBMC.

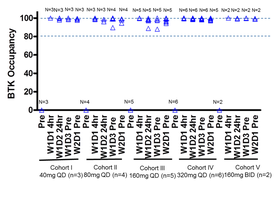


Figure 4. Lymph Node.

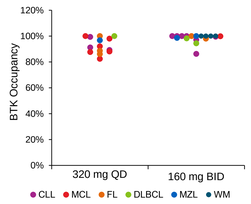
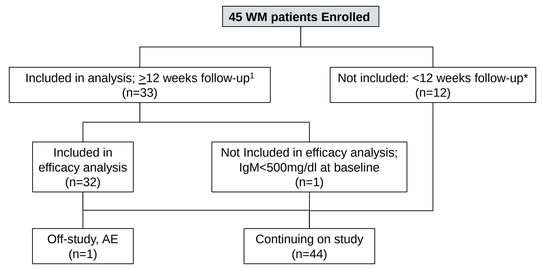


Figure 5. Disposition.



* As of 3 October 2016 data cut-off.

Table 2: Patient characteristics.

Characteristic	Total (N=33)
Age, median (range)	66 (44-82)
ECOG Performance Status:	
0	11 (33%)
1	22 (67%)
2	0
Follow-up, Months, Median (range)	9.6 (3.0- 24.7)
Prior Treatment Status	
Treatment-naive	5
Relapsed/ refractory	28
Number of prior therapies, Median (range)	2 (1-8)
Rituximab-refractory* (% R/R pts)	17 (61%)
Genotype:	
$MYD88^{L265P}$/ $CXCR4^{WT}$	19
$MYD88^{L265P}$/ $CXCR4^{WHIM}$	2
$MYD88^{WT}$	3
Unavailable	9

* Failure of response to, or progression within 12 months of, rituximab-based therapy

Table 3: Most frequent AEs (>10%) independent of causality.

	All Grade		Grade 3-4	
	n (pts)	% (n=33)	n (pts)	% (n=33)
Upper respiratory tract infection	13	39%	0	0%
Petechiae/ purpura/ contusion	11	33%	0	0%
Nausea	8	24%	0	0%
Diarrhea	8	24%	1	3%
Constipation	7	21%	0	0%
Headache	6	18%	1	3%
Anemia	5	15%	4	12%
Rash	5	15%	0	0%
Neutropenia	4	12%	2	6%
Back pain	4	12%	0	0%
Urinary tract infection	4	12%	0	0%

Table 4: Adverse events of significance.

	All Cause	
AEs of Significance	n (pts)	% (n=33)
Patients with at least one AE ≧Grade 3	16	48%*
Patients with at least one SAE	12	36%†
Events leading to treatment discontinuation	1§	3%

* Grade ≥3 events considered possibly related to BGB-3111: neutropenia (n=2), diarrhea, hypertension, pneumonia, increased LFTs, cryptococcal meningitis, pulmonary hypertension, vomiting (all n=1).
† SAE considered possibly related to BGB-3111: atrial fibrillation, cryptococcal meningitis, pneumonia, vomiting (all n=1).
§ Bronchiectasis.

Table 5: Adverse events of special interest.

	All Grade		Grade 3-4	
AEs of Special Interest	n (pts)	% (n=33)	n (pts)	% (n=33)
Diarrhea	8	24%	1	3%
Serious hemorrhage*	0	0%	0	0%
Atrial fibrillation	3†	9%	0	0%

* Grade ≥3 hemorrhage, or CNS hemorrhage of any grade.
† 2 patients had pre-existing atrial fibrillation.

Table 6: Modified IWWM response criteria.

Category	Criteria
Complete Response (CR)	• Normal serum IgM values • Disappearance of monoclonal protein by immunofixation • No histological evidence of bone marrow involvement • Complete resolution of lymphadenopathy/splenomegaly (if present at baseline)
Very Good Partial Response (VGPR)	• ≥90% reduction of serum IgM from baseline or normal IgM values • Reduction in lymphadenopathy/splenomegaly (if present at baseline)
Partial Response (PR)	• ≥50% reduction of serum IgM from baseline • Reduction in lymphadenopathy/splenomegaly (if present at baseline)
Minor Response (MR)	• At least 25% but <50% reduction of serum IgM from baseline
Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive Disease (PD)	At least one of the following: • Confirmed ≥25% increase in serum IgM and total increase of ≥500 mg/dL from nadir (on treatment) • New lymph nodes >1.5 cm, or ≥50% increase from nadir in SPD of >1 node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis • New splenomegaly or ≥50% increase from nadir in enlargement • New extranodal disease • New or recurrent involvement in bone marrow • New symptomatic disease

Table 7: Efficacy Summary (n=32).

	Total
Median follow-up (range)	9.6 months (3.0- 24.7 months)
Best Response (n=32):	
CR	0
VGPR	11 (34%)
PR	14 (44%) — **78%***
MR	5 (16%) — **94%†**
SD	2 (6%)
IgM reduction (median, %)	32.5 g/L to 4.0 g/L (88%)
Hemoglobin Change (median)	10.3 g/dl to 13.6 g/dl
Lymphadenopathy Reduction by CT (#pts, range)	12/12 (9-100%)

* Major response rate.
† Overall response rate.

Figure 5. IgM and HGB levels (median).

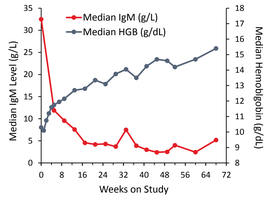


Figure 6. IWWM Response over time on treatment.

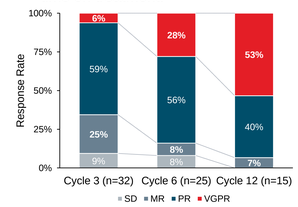


Figure 7. Progression-Free Survival.

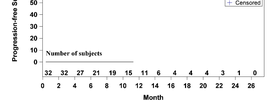
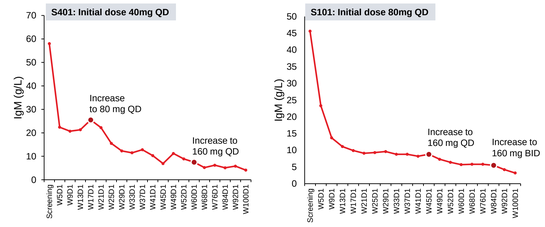


Table 8. Response rate by *MYD88* mutation status: Preliminary results (n=23*).

	Best Response			
	VGPR	PR	MR	SD
$MYD88^{L265P}$/ $CXCR4^{WT}$ (n=18)	8 (44%)	7 (39%)	2 (11%)	1 (6%)
$MYD88^{L265P}$/ $CXCR4^{WHIM}$ (n=2)	0	1 (50%)	1 (50%)	0
$MYD88^{WT}$ (n=3)	0	1 (33%)	1 (33%)	1 (33%)

* Patients evaluable for response

Figure 8. Intrapatient dose escalation.



Conclusions

- The highly selective and orally bioavailable BTK inhibitor BGB-3111 achieves high plasma concentrations and complete BTK occupancy in blood and lymph nodes
- Remains highly tolerable despite exposure and occupancy advantages:
  - One AE-related death (due to pre-existing bronchiectasis, in patient in VGPR)
- Highly active in WM:
  - Response rate 94%, with 34% VGPR
  - No progressive disease to date
- A Ph 3 trial comparing BGB-3111 to ibrutinib in WM is planned