A Head-to-Head Phase 3 Study Comparing BGB-3111 and Ibrutinib in Patients With Waldenström Macroglobulinemia

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Author Disclosures

- C Tam have no relevant financial relationships to disclose.
- C Buske: Roche, Janssen
- V LeBlond: Roche, Janssen, AbbVie, Gilead, Servier
- W Novotny, S Atwal, A Cohen, J Huang: Employed by BeiGene
- R Owen: Pharmacyclics, Acerta, Janssen
- A Tedeschi: Janssen, Gilead

Background (1)

- WM is a rare B-cell malignancy, characterized by bone marrow infiltration with monoclonal IgM-secreting lymphoplasmacytic cells[1]
- The incidence is roughly 3 cases per million, with approximately 1000-1500 new patients diagnosed in the USA annually[2]
- Most WM patients (>90%) have a recurrent somatic activating mutation of the *MYD88* gene (*MYD88*^{L265P}) that triggers downstream IRAK-mediated NF-kB signaling supporting WM cell survival[3,4]
- Bruton's tyrosine kinase (BTK), a critical signaling component of the B-cell receptor pathway, is constitutively activated in WM and has been shown to be a key mediator in tumor cell survival[4-6]

[1] Castillo JJ, et al. *Br J Haematol*. 2016;92(2):209-217; [2] American Cancer Society. Available at: https://www.cancer.org/cancer/waldenstrom-macroglobulinemia/about/key-statistics.html. [3] Treon SP, et al. *N Engl J Med*. 2012;367:826-833; [4] Yang G, et al. *Blood*. 2013;122:1222-1232. [5] Treon SP, et al. *Blood*. 2014;123:2791-2796; [6] Argyropoulos KV, et al. *Leukemia*. 2016;30:1116-1125.

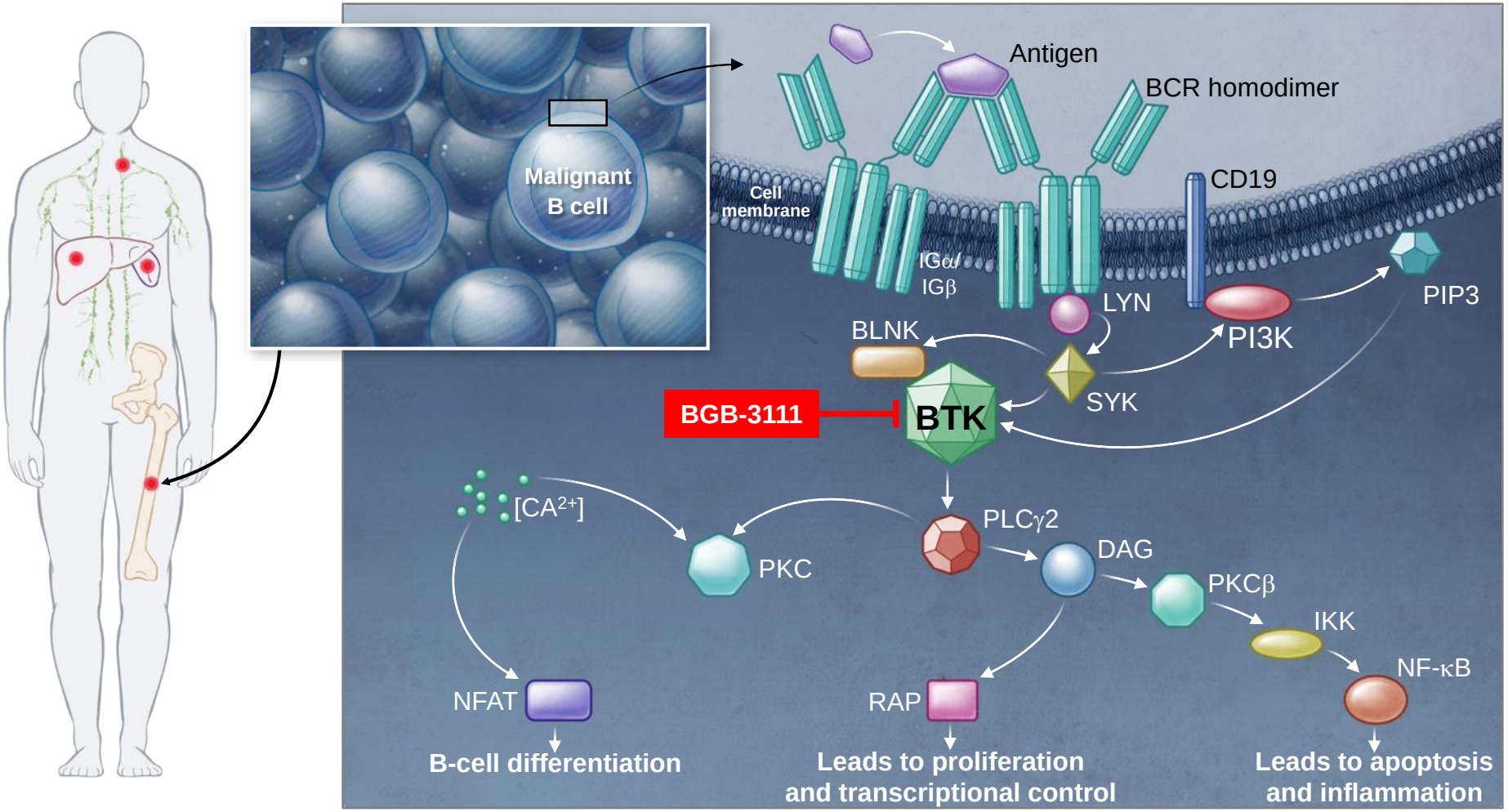
Background (2)

- Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies, including WM, particularly WM harboring the *MYD88*^{L265P} mutation (*MYD88*^{MUT})[1]
- Ibrutinib, the first-generation BTK inhibitor, has shown activity in WM[2,3]
  - Major response rate: 73% (including 16% VGPR)[2]
  - 68% 3-year event-free survival[3]
- BGB-3111 is a potent and specific BTK inhibitor, designed to minimize off-target inhibition of TEC- and EGFR-family kinases

VGPR, very good partial response

[1] Treon SP, et al. *N Engl J Med*. 2015;373:584-586; [2] Treon SP, et al. *N Engl J Med*. 2015;372:1430-1440. [3] Palomba ML, et al. IWWM. 2016 [abstract].

BGB-3111 Mechanism of Action



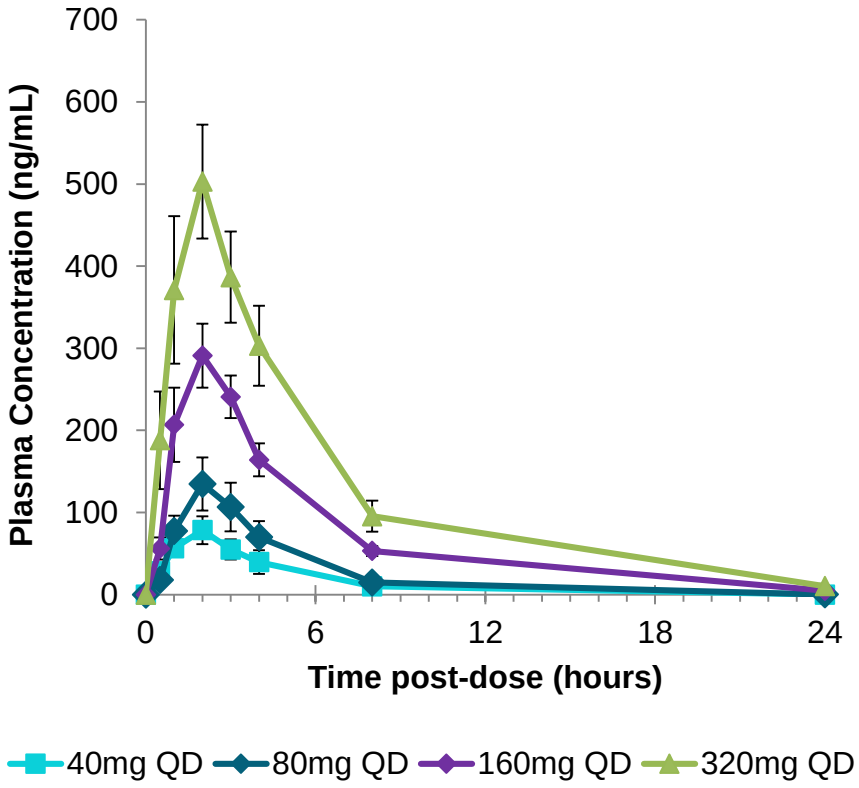
BGB-3111: Kinase Selectivity Relative to Ibrutinib

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

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-$PLC_{\gamma 1}$ 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

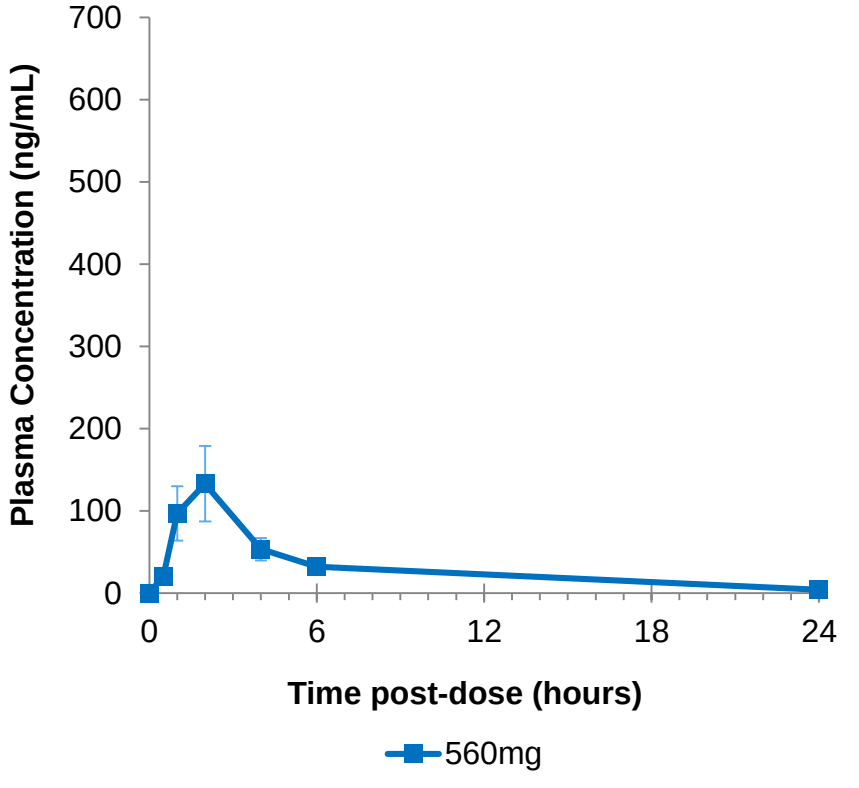
Plasma Exposure Comparison for BGB-3111 & Ibrutinib

BGB-3111



Tam *et al.*, ASH, 2015

Ibrutinib



Adapted from Advani *et al.*, JCO, 2013

- 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

Rationale and Objective

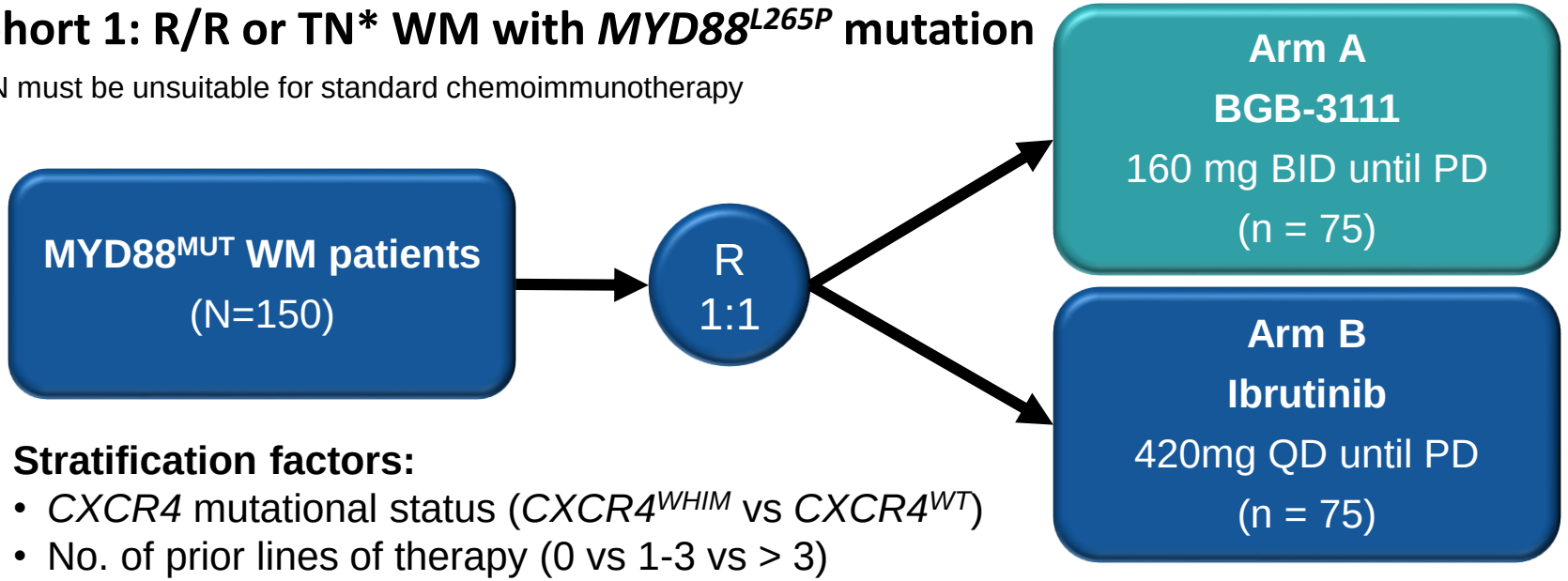
- Initial results from an ongoing phase 1 trial suggested encouraging clinical activity for BGB-3111 in patients with WM
  - Overall response rate: 90%
  - Major response rate: 76% (including 43% VGPR)
  - Response depth improved over time
- Early safety data suggested a tolerable safety profile
  - No unanticipated safety signals based on the known profile of BTK inhibition in WM
  - To date: No treatment discontinuation due to BGB-3111 related toxicity
  - One AE-related death (due to pre-existing bronchiectasis, while in VGPR)

- **Primary objective:** compare the efficacy of BGB-3111 versus ibrutinib in patients with *MYD88*^{L265P} WM as measured by rate of CR or VGPR, according to an adaptation of the Sixth IWWM criteria based on independent review

BGB-3111 vs Ibrutinib Phase 3 Study Design

Cohort 1: R/R or TN* WM with *MYD88*^{L265P} mutation

*TN must be unsuitable for standard chemoimmunotherapy



Stratification factors:

- *CXCR4* mutational status (*CXCR4*^{WHIM} vs *CXCR4*^{WT})
- No. of prior lines of therapy (0 vs 1-3 vs > 3)

Cohort 2: WM with wild type MYD88; present in ~10% of enrolled patients

This study is registered at ClinicalTrials.gov (NCT03053440)

Key Eligibility Criteria

Key Inclusion Criteria:

- Measurable WM (IgM > 0.5g/dL)
- TN WM must be considered unsuitable for standard chemoimmunotherapy
- Age ≥ 18 years
- ECOG PS 0-2
- Neutrophils ≥ 0.75 x 10^9/L*
- Platelets ≥ 50 x 10^9/L†
- AST and ALT ≤ 3 × ULN
- CrCl ≥ 30 ml/min by Cockcroft-Gault or eGFR
- Post-SCT relapse must be ≥ 3 mos after ASCT or ≥ 6 mos after alloSCT

Key Exclusion Criteria:

- Prior BTK exposure
- Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia, CHF, any Class 3 or 4 cardiac disease (congestive heart failure) as defined by NYHA
- QTcF prolongation (> 480 msec)
- Any medications that are strong or moderate cytochrome P450, CYP3A inhibitors, or strong CYP3A inducers

* Independent of growth factor support within 7 days of study entry; † Independent of growth factor support or transfusion within 7 days of study entry.

Primary and Secondary Endpoints (Cohort 1)

Primary Endpoint

- Proportion of patients with CR or VGPR[1,2] by independent assessment*

Secondary Endpoints (Efficacy)

- Major response rate: CR, VGPR, or PR
- CR or VGPR by investigator assessment
- Duration of response: CR/VGPR and MRR
- PFS
- Resolution of treatment-precipitating symptoms
- Anti-lymphoma effect: reduction at any time in bone marrow involvement by lymphoplasmacytoid lymphocytes and/or size of lymphadenopathy and/or hepatosplenomegaly by CT scan

Secondary Endpoints (Safety)†

- Incidence, timing, and severity of TEAEs, according to CTCAE v4.03
- The incidence of AEs of special interest including:
  - Grade >3 diarrhea
  - Severe bleeding (grade ≥3 bleeding of any site or CNS bleeding of any grade
  - Any grade new-onset atrial fibrillation
  - Any grade pneumonitis
  - Incidence, severity, timing, and causation of AEs leading to study drug discontinuation

* The primary efficacy analysis will be conducted 9 months after the last patient is randomized.
† All patients will be followed for AEs until 30 days after the last dose of study drug.
[1] Owen RG, et al. Br J of Haematol, 2013;160:171-176. [2] NCCN. Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma. 2015;v2.

Exploratory Endpoints

- Efficacy of BGB-3111 in patients with *MYD88*^{WT} WM (Cohort 2)
- Safety of BGB-3111 in patients with *MYD88*^{WT} WM (Cohort 2)
- Impact of CXCR4 mutation status on MRR and time-to-major response in patients with *MYD88*^{L265P} WM (Cohort 1)
- OS of BGB-3111 vs ibrutinib in *MYD88*^{L265P} WM subjects (Cohort 1)
- BGB-3111 PK (Arms A and C)
- TTNT for BGB-3111 vs ibrutinib (Cohort 1)
- QoL for BGB-3111 vs ibrutinib (Cohort 1)
- Explore mechanisms of disease resistance in WM subjects who fail to respond and in those who manifest disease relapse

Study Status

- This study opened to accrual on January 25, 2017 and is currently recruiting patients from approximately 70 participating sites throughout the European Union, Asia-Pacific, and North America

Acknowledgments

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