MAJOR RESPONSES IN *MYD88* WILDTYPE (*MYD88^{WT}*) WALDENSTRÖM MACROGLOBULINEMIA (WM) PATIENTS TREATED WITH BRUTON TYROSINE KINASE INHIBITOR ZANUBRUTINIB (BGB-3111)

Abstract PF487

ASPEN
Phase 3 Waldenström Macroglobulinemia

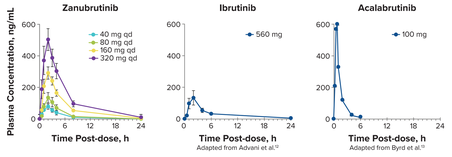
Meletios A. Dimopoulos,[1] Stephen Opat,[2,3] Hui-Peng Lee,[4] Gavin Cull,[5,6] Shirley D'Sa,[7] Roger Owen,[8] Alessandra Tedeschi,[9] Ramón García Sanz,[10] Marzia Varettoni,[11] Christian Buske,[12] Veronique LeBlond,[13] Wai Y. Chan,[14] Jingjing Schneider,[14] Muhtar Osman,[14] Aileen Cohen,[14] Jane Huang,[14] and Constantine S. Tam[15,16,17,18]

[1]General Hospital of Athens, Athens, Greece; [2]Monash Health, Clayton, Victoria, Australia; [3]Monash University, Clayton, Victoria, Australia; [4]Flinders Medical Centre, Adelaide, Australia; [5]Sir Charles Gairdner Hospital, Perth, Australia; [6]University of Western Australia, Perth, Australia; [7]University College London Hospital Foundation Trust, London, United Kingdom; [8]St James University Hospital, Leeds, United Kingdom; [9]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [10]Hospital Universitario de Salamanca, Salamanca, Spain; [11]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [12]Universitätsklinikum Ulm – CCC Ulm, Ulm, Baden-Württemberg, Germany; [13]Pitié Salpêtrière Hospital, Paris, France; [14]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [15]Peter MacCallum Cancer Center, Melbourne, Victoria, Australia; [16]St Vincent's Hospital, Fitzroy, Victoria, Australia; [17]University of Melbourne, Melbourne, Victoria, Australia; [18]Royal Melbourne Hospital, Parkville, Victoria, Australia

INTRODUCTION

- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
  - BTK is constitutively activated in WM and is a key mediator in cell survival[4,5]
- Most patients (pts) with WM (>90%) have a somatic activating mutation of the *MYD88* gene (most commonly *MYD88^{L265P}*)[3,4]
- BTK inhibitor ibrutinib has shown activity in WM and has become a standard of care[6,7]
  - However, lower response rates,[8] no major responses,[8,9] and shorter survival[10] have been reported in pts who lack *MYD88^{L265P}* or other activating mutations (*MYD88^{WT}*)
- Effective treatments for *MYD88^{WT}* pts with WM are needed
- Zanubrutinib (BGB-3111) is an investigational, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
  - Has been shown to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous pharmacokinetic/pharmacodynamic properties[11] (**Figure 1**)
  - Complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes[11] (**Figure 2**)

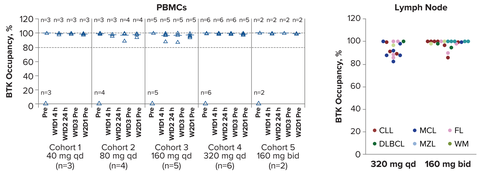
Figure 1. Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib



Adapted from Advani et al.[12]

qd, once daily.
Note: these data are from 3 separate analyses and differences in studies should be considered.

Figure 2. Sustained BTK Inhibition in Peripheral Blood and Lymph Nodes



Complete and sustained BTK occupancy is seen in paired PBMC (left figure) and lymph node biopsy samples (right figure) collected predose on day 3. In blood samples, complete BTK occupancy was seen at the lowest dose (40 mg). Note 100% median trough occupancy at a dose of 160 mg twice daily, with 94% of pts having >90% occupancy in lymph nodes across malignancies.
bid, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PBMC, peripheral blood mononuclear cell; Pre, predose; W, week; WM, Waldenström macroglobulinemia.

- Based on drug interaction studies:
  - Co-administration with strong or moderate CYP3A inhibitors (including agents such as azole anti-fungals, important in the management of pts with leukemia/lymphoma) is permitted at a reduced dose
  - Co-administration of proton pump inhibitors or other gastric acid-reducing agents does not affect zanubrutinib exposure
  - Pts have been allowed to receive anticoagulant or antiplatelet agents on zanubrutinib trials
- In the Phase 1/2 study of zanubrutinib in B-cell malignancies (NCT02343120, BGB-3111-AU-003):
  - In *MYD88* unselected WM[14] (n=73) [updated results to be presented, Poster PF481]
    - Overall response rate (ORR) 91.8%; very good partial response (VGPR) 41.4%
  - In *MYD88^{WT}* WM[14] (n=9)
    - ORR 88.9%, major response rate (MRR; partial response or better) 66.7%, VGPR 22.2%

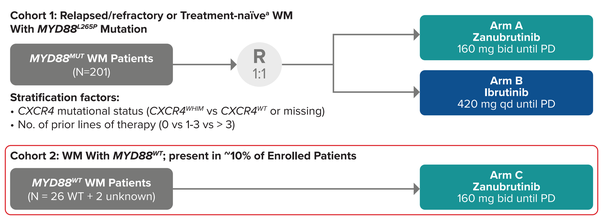
OBJECTIVE

- To assess the safety and efficacy of zanubrutinib in WM pts with *MYD88^{WT}* from an exploratory cohort of the ongoing phase 3 study of zanubrutinib vs ibrutinib in pts with WM (ASPEN; NCT03053440)

METHODS

- Open-label, multicenter, randomized, phase 3 study of zanubrutinib vs ibrutinib in pts with WM (**Figure 3**)

Figure 3. Phase 3 ASPEN Trial Design



bid, twice daily; PD, progressive disease; qd, once daily; R/R, relapsed/refractory; TN, treatment-naive. *EUDRACT 2016-002980-33; NCT03053440*
[a]TN must be unsuitable for standard chemoimmunotherapy.

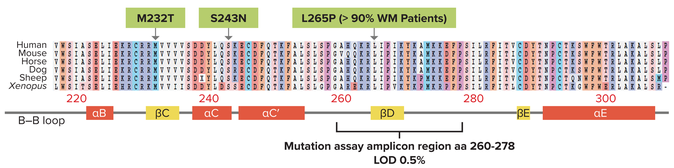
Eligibility

- Clinical and definitive histologic diagnosis of WM, with measurable disease (serum IgM level >0.5 g/dL), and meeting ≥1 criterion for treatment according to consensus panel criteria from the Seventh IWWM[15]
- If treatment-naïve, must be considered by treating physician unsuitable for standard chemoimmunotherapy regimens
- Eastern Cooperative Oncology Group performance status 0-2
- Absolute neutrophil count ≥750/μL, platelets ≥50 000/μL (independent of growth factor/transfusions)
- Adequate renal, hepatic, and coagulation function
- No significant cardiac disease, active central nervous system involvement, or prior BTK inhibitors

Cohort Assignment

- Bone marrow *MYD88* and *CXCR4* mutations were assessed centrally at study entry (NeoGenomics Laboratory, California, USA)[15]
  - The *MYD88* mutation assay used detects all mutations in the region encompassing amino acid Ala^{260}- Pro^{278}, which includes the predominant mutation in WM, *MYD88^{L265P}* (**Figure 4**)
- Pts were assigned to cohort 1 (*MYD88* mutated; randomized) or exploratory cohort 2 (*MYD88^{WT}* or *MYD88* unknown, nonrandomized) based on the central laboratory *MYD88* mutation assay results

Figure 4. *MYD88* Activating Mutations in WM Patients



Adapted from Ngo et al[17] and Treon et al[15]
LOD, limit of detection; WM, Waldenström macroglobulinemia.

- Mutation detection in the *MYD88* amplicon (Ala^{260}-Pro^{278}) by the NeoGenomics LDT assay includes a wild-type–allele-blocking approach (limit of detection [LOD] 0.5%)[15] versus standard PCR/bidirectional Sanger sequencing assay used to detect *CXCR4* mutations (LOD, 10%-15%)
- For *MYD88^{WT}* pts with available samples (12 of 26), *MYD88* mutations were also evaluated by next-generation sequencing (200x, LOD 5%) - no other activating mutations were detected

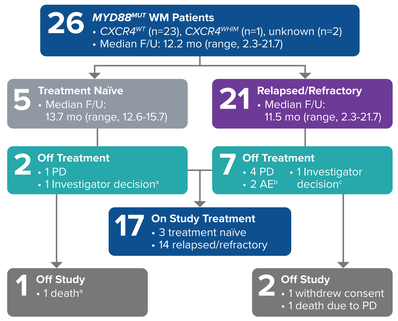
Exploratory End Points for Cohort 2

- Responses were assessed monthly by IgM with extramedullary disease assessment every 3 months, according to response criteria in the NCCN WM guidelines[18] and modified Owen criteria[19] as assessed by the investigator
- Efficacy: response rates (overall and major response rate), duration of response, progression-free survival, overall survival
- Safety assessed according to NCI-CTCAE v4.03

RESULTS

- Twenty-six *MYD88^{WT}* WM pts were enrolled, including 5 treatment-naïve pts, with a median follow-up of 12.2 mo (range, 2.3-21.7; **Figure 5** and **Table 1**)

Figure 5. Patient Disposition



Data cutoff: 28 February, 2019.
AE, adverse event; F/U, follow-up; PD, progressive disease.
[a]Pt discharged to hospice for palliative care, and deceased due to unrelated cardiac failure (onset date was 32 days from the last dose received).
[b]Grade 4 subdural hemorrhage; grade 3 diarrhea.
[c]Investigator decided no further treatment needed.

Table 1. Patient and Disease Characteristics

Characteristic	Total (N=26)
Age, median (range), y	71.5 (39-87)
Sex, n (%)	
Men	14 (53.8)
Women	12 (46.2)
ECOG PS, n (%)	
0	9 (34.6)
1	14 (53.8)
2	3 (11.5)
Prior treatment status	
Treatment-naïve, n (%)	5 (19.2)
R/R, n (%)	21 (80.8)
No. of prior therapies for R/R pts, median (range)	1 (1-5)
Extramedullary disease present at baseline	13 (50.0)
Genotype, n (%)	
MYD88^{WT}/CXCR4^{WT}	23 (88.5)
MYD88^{WT}/CXCR4^{WHIM}	1 (3.8)
MYD88^{WT}/CXCR4 unknown	2 (7.7)

ECOG PS, Eastern Cooperative Oncology Group performance status; R/R, relapsed/refractory.

Safety

- Most common AEs (in >15% pts) were contusion, constipation, diarrhea, hypertension, muscle spasm, pneumonia, and upper respiratory tract infection (**Figure 6**)

Figure 6. Common Adverse Events (>10% Patients), Regardless of Causality

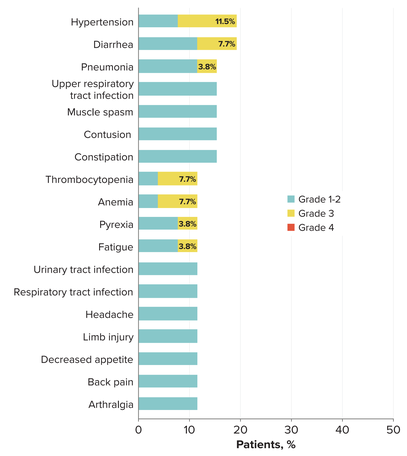


Table 2. Adverse Events Overview

Treatment-Emergent AE	n (%)
Patients with ≥1 AE grade ≥3	12 (46.2)
Patients with ≥1 serious AE	8 (30.8)
AE leading to treatment discontinuation	2[a] (7.7)
Fatal AE	0
AE of interest (BTK inhibitor class)	
Bleeding of any grade	9 (34.6)
Most commonly grade 1 contusion	4 (15.4)
Diarrhea	5 (19.2)
Hypertension	5 (19.2)
Grade 3 or 4 cytopenia	4 (15.4)
Grade 3 or 4 infections	3 (11.5)
Second malignancy[b]	3 (11.5)
Major hemorrhage[c]	2 (7.7)
Atrial fibrillation/flutter	0

AE, adverse event; SAE, serious adverse event.
[a]Grade 4 subdural hemorrhage (related) and grade 3 diarrhea (related).
[b]Basal cell carcinoma (n=2) and Queyrat erythroplasia (n=1).
[c]Defined as any-grade ≥3 hemorrhage or any-grade CNS hemorrhage: gastric ulcer hemorrhage; 1 pt had periorbital hematoma, subdural hematoma, and subdural hemorrhage.

- 2 pts discontinued due to AEs
  - Grade 4 subdural hemorrhage
  - Grade 3 diarrhea
- Major hemorrhage occurred in 2 pts (**Table 2**)
  - Gastric ulcer hemorrhage
  - Periorbital hematoma, subdural hematoma, and subdural hemorrhage; treatment was permanently discontinued per protocol
- No fatal treatment emergent AEs or atrial fibrillation/flutter events have been reported

Efficacy

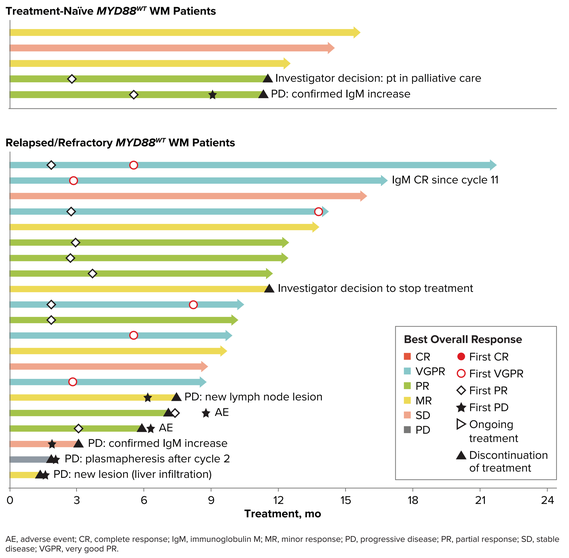
- Median time to first major response (partial response or better, requiring reduction in extramedullary disease if present at baseline) was 2.9 mo (**Figure 7** and **Table 3**)
- IgM complete response (requiring normal IgM and immunofixation negative) achieved in 1 pt
- Median progression-free survival and overall survival not yet reached (**Figure 8**)

Table 3. Best Responses

Best Response, n (%)	Total (n=26)	TN Patients (n=5)	R/R Patients (n=21)
Overall response rate (ORR)	**21 (80.8)**	**4 (80.0)**	**17 (81.0)**
Major response rate (MRR, PR or better)	**14 (53.8)**	**2 (40.0)**	**12 (57.1)**
VGPR	6 (23.1)[a,b]	0	6 (28.6)[a,b]
PR	8 (30.8)[b]	2 (40.0)	6 (28.6)
MR	7 (26.9)	2 (40.0)	5 (23.8)
SD	4 (15.4)	1 (20.0)	3 (14.3)
PD	1 (3.8)	0	1 (4.8)
Time to major response (≥PR), median (range), mo			
	2.9 (1.9-7.4)	4.2 (2.9-5.6)	2.8 (1.9-7.4)
Study follow-up time, median (range), mo			
	12.2 (2.3-21.7)	13.7 (12.6-15.7)	11.5 (2.3-21.7)

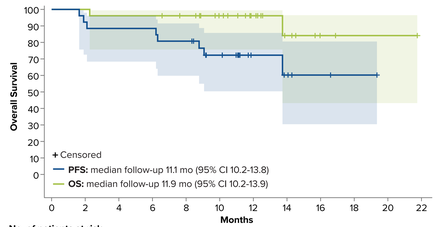
CR, complete response; IgM, immunoglobulin M; MR, minor response; MRR, major response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.
[a]One pt achieved IgM complete response (normalized IgM and negative immunofixation since cycle 11, with bulky extramedullary disease improving).
[b]Including pts confirmed by next-generation sequencing of no other activating *MYD88* mutations: 3 of 6 VGPR (including IgM CR); 3 of 8 PR.

Figure 7. Responses Over Time on Treatment



AE, adverse event; CR, complete response; IgM, immunoglobulin M; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

Figure 8. Progression-free and Overall Survival



Shaded areas show the 95% CI.

CONCLUSIONS

In this exploratory analysis of *MYD88^{WT}* WM pts (n=26):

- Single-agent major response activity (including VGPR) observed
  - MRR of 53.8% including 23.1% with VGPR
  - IgM CR achieved in 1 pt
  - Median time to first major response was 2.9 mo (range, 1.9-7.4)
- Zanubrutinib was generally well tolerated
  - Discontinuation due to AEs occurred in 7.7% of pts (2 of 26)
  - Primary reason for discontinuation was PD: 3 of 5 within first 3 cycles
  - No fatal AEs and no events of atrial fibrillation reported
- The depth and durability of response in pts with *MYD88^{WT}* WM will be further assessed in this ongoing phase 3 study

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DISCLOSURES

MAD: honoraria from Celgene, Amgen, BMS, Takeda, Janssen; consulting/advisory role with Celgene, Amgen, BMS, Takeda, Janssen. **SO:** honoraria from Roche, Janssen, Celgene, Takeda, AbbVie, Gilead, Merck, and Mundipharma; consulting/advisory role with Roche, Janssen, Celgene, Takeda, AbbVie, Gilead, Merck, Mundipharma, and Novartis; research funding from BeiGene, Roche, Janssen, AbbVie, Takeda, Merck, Gilead, Epizyme. **HL:** stock options with CSL; honoraria and advisory board with Janssen and MSD. **GC:** travel expenses from Amgen, Takeda, AbbVie and Roche; research funding from BeiGene. **SD:** honoraria with Amgen; honoraria, speaker's bureau and travel expenses with Janssen. **RO:** honoraria with Celgene; honoraria, consulting/advisory role and travel expenses with Janssen. **AT:** honoraria with AbbVie, Janssen, Sunesis, Gilead, BeiGene; consulting/advisory role with AbbVie, Janssen, Sunesis. **RGS:** honoraria from Janssen, Takeda, Amgen, BMS; consulting/advisory role with Janssen, Takeda, Amgen, BMS; research funding from Gilead, Incyte; patents from Eurocloanality (IVS); travel expenses from Janssen, Takeda. **MV:** consulting/advisory role with Janssen, Roche; travel expenses from Gilead, AbbVie, Janssen. **CB:** honoraria, consulting/advisory role and speaker's bureau with Roche, Janssen, Celltrion and BeiGene; Research funding from Roche, Janssen and BeiGene; **VL:** honoraria from Roche, Janssen, Gilead, Abbvie, Amgen; consulting/advisory role with Roche, Janssen, AbbVie; speaker's bureau with AbbVie, Janssen Roche; travel expenses from AbbVie, Roche. **JS:** employment with BeiGene, Amgen; stock options with BeiGene, Amgen, Gilead, Puma, Esperion; travel expenses from BeiGene, Amgen. **MO:** employment with Amgen, BeiGene, stock options with Amgen, Celgene, CRISPR, Editas, Illumina, BeiGene, Oncomed, Merrimack; **WYC, JH:** employment and stock options with BeiGene. **AC:** employment with BeiGene and consulting/advisory role with BeiGene and Acerta. **CST:** honoraria from BeiGene, Janssen, AbbVie, Novartis; research funding from Janssen and AbbVie

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