UPDATED RESULTS OF THE ASPEN TRIAL FROM A COHORT OF PATIENTS WITH *MYD88* WILD-TYPE WALDENSTRÖM MACROGLOBULINEMIA

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INTRODUCTION

- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
- First-generation BTK inhibitor ibrutinib has shown activity in Waldenström macroglobulinemia (WM) and has become a standard of care[4]
  - However, lower response rates,[5] no major responses,[5,6] and shorter survival[7] have been reported in patients (pts) who lack *MYD88*^{L265P} or other activating mutations (*MYD88*^{WT})
- Zanubrutinib is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases (**Figure 1**)
  - **Potent, selective, and irreversible**[8]
  - **Equipotent against BTK compared with ibrutinib**; higher selectivity vs EGFR, ITK, JAK3, HER2, and TEC[9]
  - **Advantageous pharmacokinetic/pharmacodynamic properties**: complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes[8]
  - **Favorable drug-drug interaction properties**: can be co-administered with strong/moderate CYP3A inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and anti-thrombotic agents[10,11]

Zanubrutinib (BGB-3111)

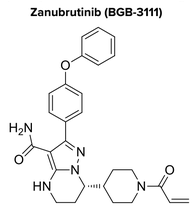
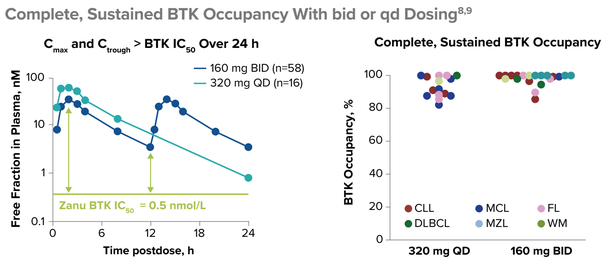


Figure 1a. Zanubrutinib: A Potent and Selective BTK Inhibitor[8,9]

	Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
ON TARGET	BTK	BTK-pY223 Cellular Assay	1.8	3.5	0.5
		Rec-1 Proliferation	0.36	0.34	1.1
		BTK Occupation Cellular Assay	2.2	2.3	1
		BTK Biochemical Assay	0.22	0.2	1.1
OFF TARGET	EGFR	p-EGFR HTRF Cellular Assay	606	101	6
		A431 Proliferation	3210	323	9.9
	ITK	ITK Occupancy Cellular Assay	3265	189	17
		p-PLCγ1 Cellular Assay	3433	77	45
		IL-2 Production Cellular Assay	2536	260	9.8
		ITK Biochemical Assay	30	0.9	33
	JAK3	JAK3 Biochemical Assay	200	3.9	51
	HER2	HER2 Biochemical Assay	661	9.4	70
	TEC	TEC Biochemical Assay	1.9	0.8	2.4

Figure 1b. Complete, Sustained BTK Occupancy With bid or qd Dosing[8,9]



BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; C_{max}, maximum concentration; C_{trough}, trough concentration; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; HER2, human epidermal growth factor receptor 2; HTRF, homogeneous time resolved fluorescence; IC_{50}, half maximal inhibitory concentration; ITK, IL-2–inducible T-cell kinase; JAK3, Janus-associated kinase 3; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PLC, phospholipase C; QD: once daily; WM, Waldenström macroglobulinemia; Zanu, zanubrutinib.

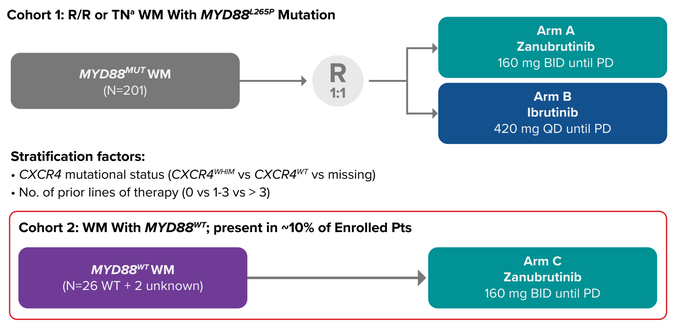
OBJECTIVE

- 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

- ASPEN is an open-label, multicenter, randomized, phase 3 study of zanubrutinib vs ibrutinib in pts with WM (**Figure 2**)

Figure 2. Phase 3 ASPEN Trial Design



EUDRACT 2016-002980-33; NCT03053440.
BID, twice daily; PD, progressive disease; pt, patient; QD, once daily; R/R, relapsed/refractory; TN, treatment-naïve.
[a]TN must be unsuitable for standard chemoimmunotherapy.

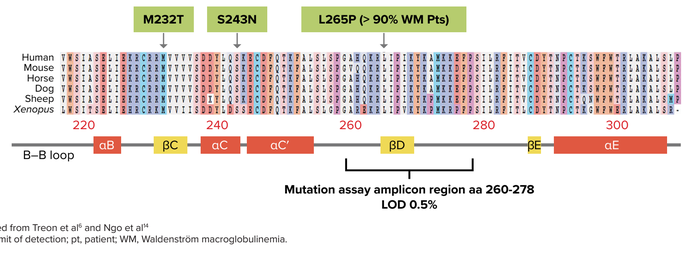
Eligibility

- Clinical and definitive histologic diagnosis of WM, with measurable disease (serum IgM >0.5 g/dL), and meeting ≥1 criterion for treatment according to consensus panel criteria from the Seventh International Workshop on WM[12]
- 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 ≥50000/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, Aliso Viejo, CA, USA)[13]
  - 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 3**)
- 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 3. *MYD88*-Activating Mutations in Pts With WM



Adapted from Treon et al[6] and Ngo et al[14]
LOD, limit of detection; pt, patient; WM, Waldenström macroglobulinemia.

- 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%)[13] versus standard polymerase chain reaction/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 (200×; LOD, 5%); no other activating mutations were detected

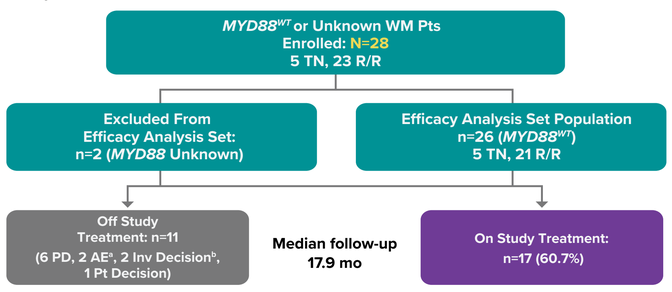
Exploratory End Points for Cohort 2

- Responses were assessed monthly by immunoglobulin M (IgM) with extramedullary disease assessment every 3 months, according to response criteria in the National Comprehensive Cancer Network WM guidelines[15] and modified Owen criteria[16] as assessed by the independent review committee
- Efficacy: response rates (overall and major response rate), duration of response, progression-free survival, and overall survival; safety assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03

RESULTS

- In total, 28 pts (n=26 *MYD88*^{WT}; n=2 *MYD88* mutation status unknown) were enrolled into cohort 2
- The safety analysis set includes all 28 pts, and the efficacy analysis set includes 26 *MYD88*^{WT} pts, with a median follow-up of 17.9 months (range, 2.3-27.8; **Figure 4** and **Table 1**)

Figure 4. Disposition of Pts in Cohort 2



Data cutoff date: 31 Aug, 2019.
AE, adverse event; F/U, follow-up; Inv, investigator; PD, progressive disease; pt, patient.
[a]Grade 4 subdural hemorrhage; grade 3 diarrhea.
[b]Investigator decided no further treatment needed (n=1); pt discharged to hospice for palliative care (n=1).

Table 1. Pt and Disease Characteristics

Characteristic	Total (N=28)
Age, median (range), y	70.1 (39-87)
>65 years, n (%)	19 (67.9)
>75 years, n (%)	12 (42.9)
Sex, n (%)	
Men	14 (50)
Women	14 (50)
IPSSWM, n (%)	
Low	5 (17.9)
Intermediate	11 (39.3)
High	12 (42.9)
Prior treatment status	
Treatment-naïve, n (%)	5 (17.9)
R/R, n (%)	23 (82.1)
No. of prior therapies for R/R pts, median (range)	1 (1-5)
Extramedullary disease present at baseline by IRC, n (%)	21 (75.0)
Genotype, n (%)	
MYD88^{WT}/*CXCR4*^{WT}	23 (82.1)
MYD88^{WT}/*CXCR4*^{WHIM}	1 (3.6)
MYD88^{WT}/*CXCR4* unknown	2 (7.1)
MYD88 unknown/*CXCR4* unknown	2 (7.1)
Hemoglobin ≤110 g/L, n(%)	15 (53.6)

IPSSWM, International Prognostic Scoring System Waldenström macroglobulinemia; IRC, independent review committee; pt, patient; R/R, relapsed/refractory.

Safety (n=28)

Table 2. AE Overview

Treatment Emergent AE	n (%)
Pts with ≥1 AE grade ≥3	18 (64.3)
Pts with ≥1 serious AE	11 (39.3)
AE leading to death	0
AE leading to treatment discontinuation	2[a] (7.1)
AE leading to dose reduction	2[b] (7.1)

AE, adverse event; pt, patient.
[a]Grade 4 subdural hemorrhage (related) and grade 3 diarrhea (related).
[b]Grade 3 pneumonitis resolved and followed by grade 2 pneumonia (n=1); grade 1 diarrhea (n=1).

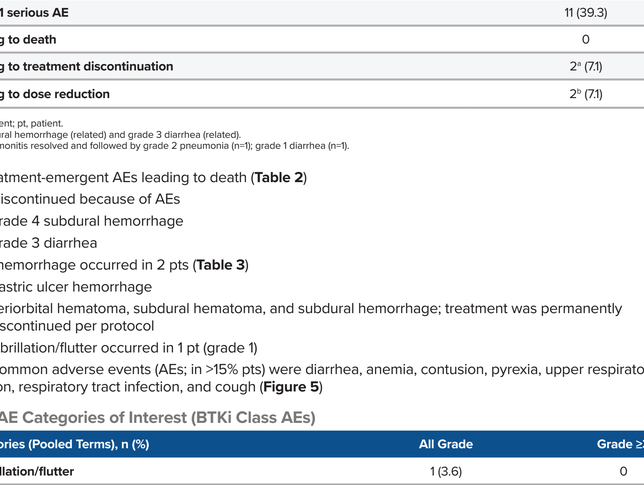
- No treatment-emergent AEs leading to death (**Table 2**)
- 2 Pts discontinued because of AEs
  - Grade 4 subdural hemorrhage
  - Grade 3 diarrhea
- Major hemorrhage occurred in 2 pts (**Table 3**)
  - Gastric ulcer hemorrhage
  - Periorbital hematoma, subdural hematoma, and subdural hemorrhage; treatment was permanently discontinued per protocol
- Atrial fibrillation/flutter occurred in 1 pt (grade 1)
- Most common adverse events (AEs; in >15% pts) were diarrhea, anemia, contusion, pyrexia, upper respiratory tract infection, respiratory tract infection, and cough (**Figure 5**)

Table 3. AE Categories of Interest (BTKi Class AEs)

AE Categories (Pooled Terms), n (%)	All Grade	Grade ≥3
Atrial fibrillation/flutter	1 (3.6)	0
Diarrhea (PT)	8 (28.6)	2 (7.1)
Hemorrhage	11 (39.3)	2 (7.1)
Major hemorrhage[a]	2 (7.1)	2 (7.1)
Hypertension	3 (10.7)	3 (10.7)
Neutropenia[b]	5 (17.9)	3 (10.7)
Infection	21 (75.0)	8 (28.6)
Second malignancy[c]	4 (14.3)	0

No tumor lysis syndrome or opportunistic infection was reported.
AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.
[a]Defined as any grade ≥3 hemorrhage or any grade central nervous system hemorrhage: gastric ulcer hemorrhage; and 1 patient had periorbital hematoma, subdural hematoma, and subdural hemorrhage.
[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.
[c]Basal cell carcinoma (n=3) and Queyrat erythroplasia (n=1).

Figure 5. Common AEs (Any Grade >10% or Grade ≥3 in >1 Pt), Regardless of Causality

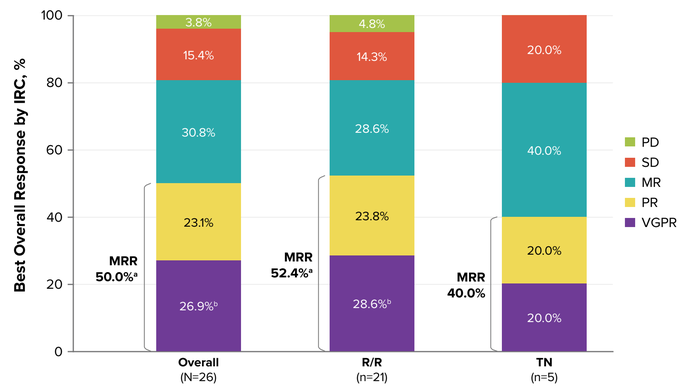


AE, adverse event; pt, patient.

Efficacy (n=26)

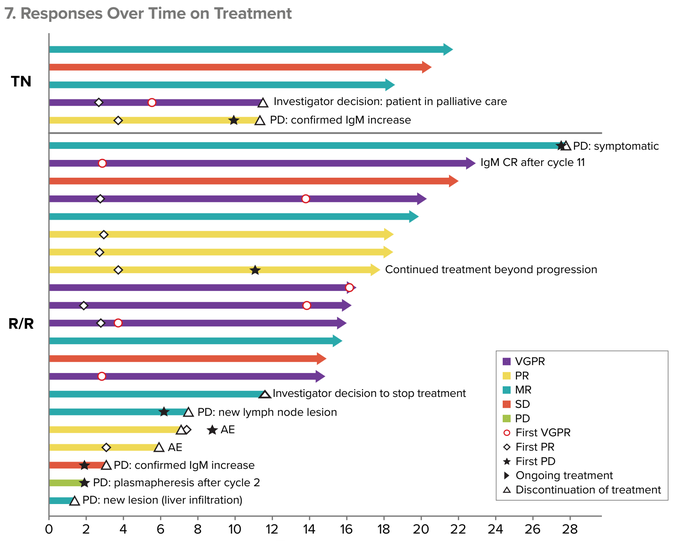
- Major response rate of 50.0% including 26.9% with VGPR (**Figure 6**)
- Median time to first major response (partial response or better, requiring reduction in extramedullary disease if present at baseline) was 2.9 mo (range, 1.9-16.1; **Figure 7**)
- IgM complete response (requiring normal IgM and immunofixation negative) was achieved in 1 pt
- Median progression-free and overall survival were not yet reached (**Figure 8**)

Figure 6. Best Responses by IRC in Patients With *MYD88*^{WT} WM



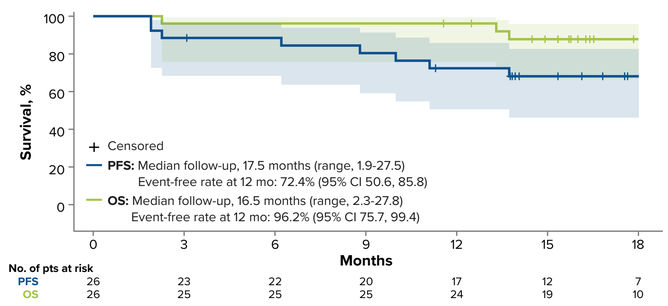
CR, complete response; IgM, immunoglobulin M; IRC, independent review committee; MR, minor response; MRR, major response rate (≥PR); PD, progressive disease; PR, partial response; pt, patient; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve; VGPR, very good PR.
[a]Including pts confirmed by next-generation sequencing of no other activating *MYD88* mutations.
[b]One pt achieved IgM complete response (normalized IgM and negative immunofixation since cycle 11, with bulky extramedullary disease improving).

Figure 7. Responses Over Time on Treatment



Note: color of bars represents the best response for each patient.
AE, adverse event; MR, minor response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve; VGPR, very good PR.

Figure 8. Progression-Free and Overall Survival



Shaded areas show the 95% CI.
OS, overall survival; PFS, progression-free survival

CONCLUSIONS

- Largest cohort of pts with WM with confirmed *MYD88*^{WT} (n=26) studied in terms of safety and efficacy of BTKi treatment
- Single-agent zanubrutinib resulted in major responses (including very good partial response)
  - Major response rate of 50.0% including 26.9% with very good partial response
  - IgM complete response achieved in 1 pt
  - Median time to first major response was 2.9 months (range, 1.9-16.1)
- Zanubrutinib was well tolerated
  - Discontinuation because of AEs occurred in 7.1% of pts (2/28)
  - Primary reason for discontinuation was progressive disease (3 of 6 within first 3 cycles)
  - No fatal AEs reported
  - Low incidences of atrial fibrillation
  - AE profile is consistent with cohort 1 finding in the ASPEN study

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