ASPEN: RESULTS OF A PHASE 3 RANDOMIZED TRIAL OF ZANUBRUTINIB VERSUS IBRUTINIB FOR PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA (WM)

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INTRODUCTION

- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling; this pathway is constitutively activated in Waldenström macroglobulinemia (WM) (>90% with *MYD88* mutations), leading to malignant cell survival[1,2]
- BTK inhibition is an emerging standard of care for WM[3]
- 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, irreversible**
  - **Equipotent against BTK compared with ibrutinib;** higher selectivity versus EGFR, ITK, JAK3, HER2, and TEC[4]
  - **Advantageous pharmacokinetic (PK)/ pharmacodynamic properties:** complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes[5]
  - **Favorable drug-drug interaction properties:** can be coadministered with strong/moderate CYP3A inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and antithrombotic agents[6,7]

Zanubrutinib (BGB-3111)

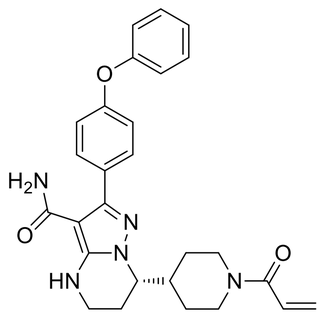
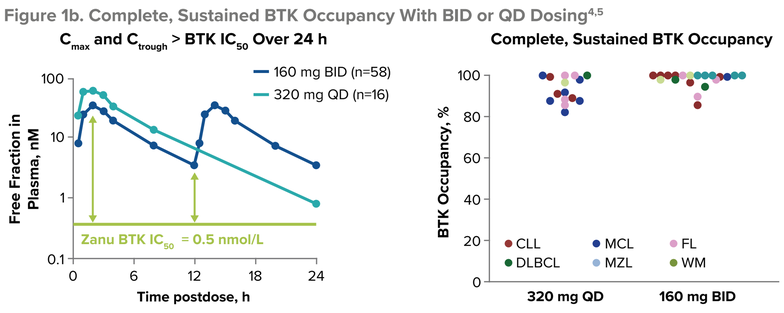


Figure 1a. Zanubrutinib: A Potent and Selective BTK Inhibitor[1,2]

	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[4,5]



Abbreviations: 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; TEC, tyrosine protein kinase Tec; WM, Waldenström macroglobulinemia; Zanu, zanubrutinib.

STUDY OBJECTIVES

Primary Objective

- To compare the efficacy of zanubrutinib versus ibrutinib
  - Primary endpoint was complete response (CR) plus very good partial response (VGPR) rate in patients with activating mutations (*MYD88*^{MUT}) WM

Secondary Objectives

- To further compare the efficacy, clinical benefit, and anti-lymphoma effects of zanubrutinib versus ibrutinib
- To evaluate safety and tolerability of zanubrutinib versus ibrutinib as measured by the incidence, timing, and severity of treatment-emergent adverse events (TEAEs) according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)

Exploratory Objectives

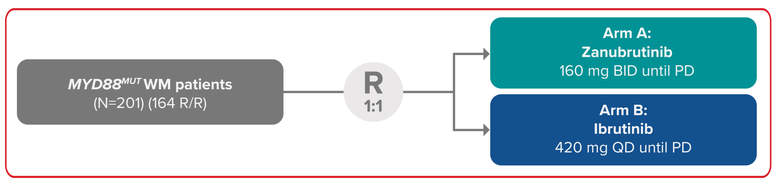
- To characterize the PK of zanubrutinib in patients with WM
- To compare quality of life (QoL) by European Organisation for Research and Treatment of Cancer QLQ-C30 and EQ-5D

METHODS

- ASPEN (NCT03053440) is an ongoing open-label, multicenter, randomized, phase 3 study designed to assess the safety, efficacy, and clinical benefit of zanubrutinib versus ibrutinib in patients with *MYD88*^{mut} WM (**Figure 2**)

Figure 2. Phase 3 ASPEN Trial Design[8]

Cohort 1: R/R or TN[a] WM With *MYD88*^{L265P} Mutation



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

Cohort 2: WM With *MYD88*^{WT}; present in ~10% of Enrolled Patients

EUDRACT 2016-002980-33; NCT03053440.
[a]TN must be unsuitable for standard chemoimmunotherapy.
Abbreviations: BID, twice daily; BTK, Bruton tyrosine kinase; *CXCR4*, C-X-C motif chemokine receptor 4; *MYD88*, myeloid differentiation primary response gene 88; MUT, mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment-naïve; WM, Waldenström macroglobulinemia; WT, wild-type.

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[8]
- 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

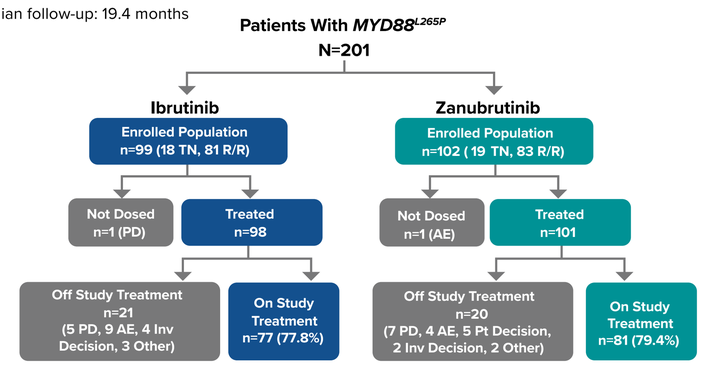
- At ASPEN study entry, *MYD88* gene mutations were assessed by a central laboratory (NeoGenomics Laboratory, Aliso Viejo, CA, USA)
- Patients with *MYD88* mutation–positive (*MYD88*$^{mut+}$) WM were randomized (1:1) to receive zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily)
  - Patients without *MYD88* mutations were assigned to a separate cohort to receive zanubrutinib; these results are reported separately

RESULTS

- Overall, 201 patients with *MYD88*$^{mut+}$ WM were randomized to receive zanubrutinib (n=102) or ibrutinib (n=99) (**Figure 3**)
- While the treatment groups were well balanced for most baseline factors, more elderly patients (>75 years, 33.3% vs 22.2%) and more patients with anemia (hemoglobin ≤110 g/L, 65.7% vs 53.5%) were randomized to receive zanubrutinib than ibrutinib (**Table 1**)
- The primary analysis results are presented here (data cutoff: August 2019), with additional follow-up data on efficacy by investigator (data cutoff: January 2020)

Figure 3. ASPEN: Disposition of Patients in Cohort 1

- Median follow-up: 19.4 months



Abbreviations: AE, adverse event; Inv, investigator; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; Pt, patient; R/R, relapsed/refractory; TN, treatment-naïve.

Table 1. ASPEN: Demographics and Disease Characteristics

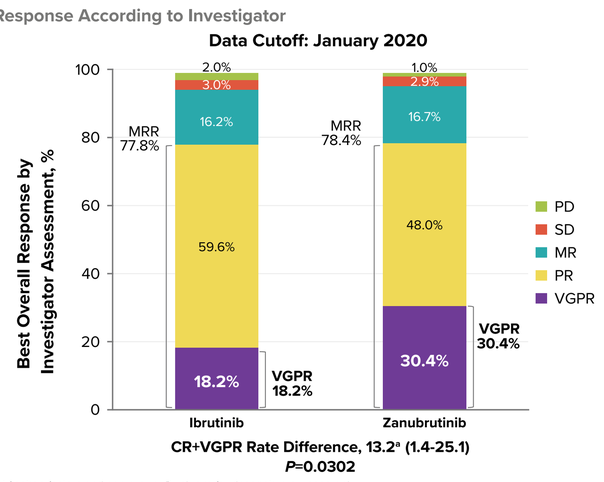
Characteristics, n (%)	Overall ITT Ibrutinib (n=99)	Overall ITT Zanubrutinib (n=102)
Age median (range), y	70.0 (38-90)	70.0 (45-87)
>65 y	70 (70.7)	61 (59.8)
>75 y	22 (22.2)	34 (33.3)
Sex, n (%)		
Male	65 (65.7)	69 (67.6)
Female	34 (34.3)	33 (32.4)
Prior lines of therapy, n (%)		
0	18 (18.2)	19 (18.6)
1-3	74 (74.7)	76 (74.5)
>3	7 (7.1)	7 (6.9)
Genotype by central lab[a], n (%)		
MYD88^{L265P}/*CXCR4*^{WT}	90 (90.9)	91 (89.2)
MYD88^{L265P}/*CXCR4*^{WHIM}	8 (8.1)	11 (10.8)
IPSS WM[9]		
Low	13 (13.1)	17 (16.7)
Intermediate	42 (42.4)	38 (37.3)
High	44 (44.4)	47 (46.1)
Hemoglobin ≤110 g/L	53 (53.5)	67 (65.7)

[a]Wild-type–blocking polymerase chain reaction for *MYD88* and Sanger sequencing for *CXCR4* using bone marrow aspirates. One patient had local next-generation sequencing testing results of *MYD88*^{L265P}/*CXCR4* Unknown.
Abbreviations: *CXCR4*, C-X-C motif chemokine receptor 4; IPSS WM, International Prognostic Scoring System for Waldenström macroglobulinemia; ITT, intention-to-treat; *MYD88*, myeloid differentiation primary response gene 88; WT, wild-type.

Efficacy

- At the primary analysis, superiority in the CR+VGPR rate of zanubrutinib compared with ibrutinib in the R/R population was not significant (descriptive *P*=0.0921)
- Area under the curve for IgM reduction over time was significantly greater for zanubrutinib versus ibrutinib (*P*=0.037)
- The VGPR rate was higher with zanubrutinib than ibrutinib (30.4% vs 18.2%; *P*=0.0302) at the additional 5-month follow-up (data cutoff: January 2020) (**Figure 4**)
  - No CRs were observed
- Subgroup analysis of CR+VGPR response rates are shown in **Figure 5**
- Progression-free survival (PFS) and overall survival (OS) were similar between patients receiving zanubrutinib and ibrutinib (**Figure 6**)

Figure 4. Response According to Investigator



[a]Adjusted for stratification factors and age group. *P*-value is for descriptive purpose only.
Abbreviations: CR, complete response; IRC, independent review committee; MRR, major response rate; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good PR.

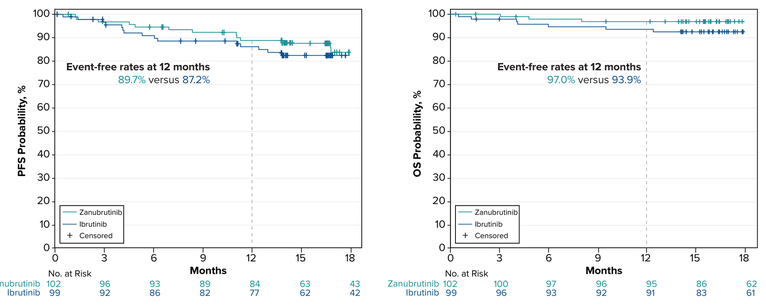
Figure 5. Forest Plot of CR+VGPR Response Rate Difference by IRC, in Overall ITT Population

Subgroup	Response/Patient Ibrutinib	Response/Patient Zanubrutinib	Rate Difference (95% CI), %
All patients	19/99	29/102	9.2 (-2.5 to 20.9)
Age Group			
≤ 65 y	5/29	12/41	12.0 (-7.5 to 31.6)
> 65 y	14/70	17/61	7.9 (-6.8 to 22.5)
Age Group			
≤ 75 y	12/77	22/68	16.8 (3.0 - 30.5)
> 75 y	7/22	7/34	-11.2 (-35.0 to 12.5)
Sex			
Male	11/65	18/69	9.2 (-4.6 to 23.0)
Female	8/34	11/33	9.8 (-11.7 to 31.3)
Treatment type by IRT			
Relapsed/Refractory	16/81	24/83	9.2 (-3.9 to 22.2)
Treatment naive	3/18	5/19	9.6 (-16.6 to 35.9)
Baseline CXCR4 mutation status by central lab			
WHIM	1/8	1/11	-3.4 (-31.9 to 25.1)
WT/UNKNOWN	18/19	28/91	11.0 (-1.5 to 23.5)
Hemoglobin			
≤110 g/L	9/53	22/67	15.9 (0.7 - 31.0)
>110 g/L	10/46	7/35	-1.7 (-19.6 to 16.1)
Baseline presence of extramedullary disease by IRC			
Yes	14/73	26/81	12.9 (-0.7 to 26.5)
No	5/26	3/21	-4.9 (-26.2 to 16.4)
WM IPSS			
High	9/44	15/47	11.5 (-6.4 to 29.3)
Intermediate	8/42	12/38	12.5 (-6.4 to 31.5)
Low	2/13	2/17	-3.6 (-28.5 to 21.3)

-100 -75 -50 -25 0 25 50 75 100

Abbreviations: CI, confidence interval; CR, complete response; *CXCR4*, C-X-C motif chemokine receptor 4; IRC, independent review committee; IRT, interactive response technology; ITT, intention-to-treat; VGPR, very good partial response; WM IPSS, Waldenström macroglobulinemia International Prognostic Scoring System; WT, wild-type.

Figure 6. PFS and OS in ITT Population



Disease progression determined by IRC.
Abbreviations: ITT, intention-to-treat; PFS, progression-free survival; OS, overall survival.

Safety

- Most patients in both treatment arms reported ≥1 AE (**Table 2**)
- Rates of atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, pneumonia, and AEs leading to discontinuation or death were lower with zanubrutinib compared with ibrutinib (**Table 3**)
  - An additional five patients in the ibrutinib arm discontinued treatment because of AEs versus zero in the zanubrutinib arm (14.3% vs 4%) with an additional 5-month follow-up (data cutoff: January 2020)
- Although the rate of neutropenia was higher with zanubrutinib (29.7% vs 13.3%), grade ≥3 infection rates were similar between treatments (17.8% vs 19.4%) (**Table 4**)
- Risk of atrial fibrillation/flutter and hypertension was lower in patients receiving zanubrutinib (**Figure 7**)
- There was a trend toward improved QoL in patients receiving zanubrutinib (**Figure 8**)

Table 2. AE Overview

Category, n (%)	Overall Ibrutinib (n=98)	Overall Zanubrutinib (n=101)
Patients with ≥1 AE	97 (99.0)	98 (97.0)
Grade ≥3	62 (63.3)	59 (58.4)
Serious	40 (40.8)	40 (39.6)
AE leading to death	4 (4.1)[a]	1 (1.0)[b]
AE leading to treatment discontinuation	9 (9.2)[c]	4 (4.0)[d]
AE leading to dose reduction	23 (23.5)	14 (13.9)
AE leading to dose held	55 (56.1)	47 (46.5)
Patients with ≥1 treatment-related AE	84 (85.7)	80 (79.2)
Patients with ≥1 AE of interest	81 (82.7)	86 (85.1)

[a]Cardiac failure acute; sepsis (n=2); unexplained death.
[b]Cardiac arrest after plasmapheresis.
[c]G5 sepsis (n=2); G5 unexplained death; G3 acute myocardial infarction; G3 hepatitis; G3 pneumonia; G2 drug-induced liver injury; G2 pneumonitis; G1 pneumonitis.
[d]G5 cardiac arrest after plasmapheresis; G4 neutropenia; G4 subdural hemorrhage; G2 plasma cell myeloma.
Abbreviations: AE, adverse event (treatment-emergent); G, grade.

Table 3. Most Common AEs

Event Preferred Term[a], n (%)	All Grades (≥20%) Ibrutinib (n=98)	All Grades (≥20%) Zanubrutinib (n=101)	Grade ≥3 (≥5%) Ibrutinib (n=98)	Grade ≥3 (≥5%) Zanubrutinib (n=101)
Diarrhea	31 (32)	21 (21)	1 (1)	3 (3)
Upper respiratory tract infection	28 (29)	24 (24)	1 (1)	0
Contusion	23 (24)	13 (13)	0	0
Muscle spasms[b]	23 (24)	10 (10)	1 (1)	0
Peripheral edema[b]	19 (19)	9 (9)	0	0
Hypertension	16 (16)	11 (11)	11 (11)	6 (6)
Atrial fibrillation[b]	14 (14)	2 (2)	3 (3)	0
Neutropenia[b]	12 (12)	25 (25)	8 (8)	16 (16)
Pneumonia[b]	12 (12)	2 (2)	7 (7)	1 (1)
Anemia	10 (10)	12 (12)	5 (5)	5 (5)
Thrombocytopenia	10 (10)	10 (9)	3 (3)	6 (5)

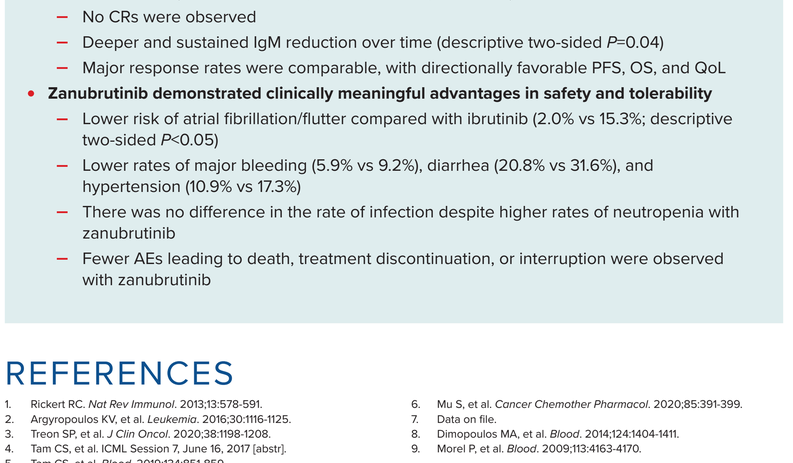
[a]Including most common AEs and AEs with ≥10% or ≥5% differentials, respectively.
[b]Descriptive two-sided *P*<0.05.
Abbreviation: AE, adverse event.

Table 4. AE Categories of Interest (BTKi Class AEs)[a]

AE Categories, n (%) (Pooled Terms)	All Grades Ibrutinib (n=98)	All Grades Zanubrutinib (n=101)	Grade ≥3 Ibrutinib (n=98)	Grade ≥3 Zanubrutinib (n=101)
Atrial fibrillation/flutter[b]	**15 (15.3)**	2 (2.0)	4 (4.1)	0 (0.0)
Diarrhea (PT)	**31 (31.6)**	21 (20.8)	1 (1.0)	3 (3.0)
Hemorrhage	**58 (59.2)**	49 (48.5)	8 (8.2)	6 (5.9)
Major hemorrhage[c]	9 (9.2)	6 (5.9)	8 (8.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)	**12 (12.2)**	6 (5.9)
Neutropenia[b,d]	13 (13.3)	**30 (29.7)**	8 (8.2)	**20 (19.8)**
Infection	66 (67.3)	67 (66.3)	19 (19.4)	18 (17.8)
Second malignancy	11 (11.2)	12 (11.9)	1 (1.0)	2 (2.0)

[a]Data cutoff, August 2019.
[b]Descriptive two-sided *P*<0.05.
[c]Defined as any grade ≥3 hemorrhage or any grade central nervous system hemorrhage.
[d]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.
Abbreviations: AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.

Figure 7. Time to AE: Risk Analysis Over Duration of Treatment



[a]Descriptive purpose only.
Abbreviation: AE, adverse event.

Figure 8. Quality of Life: Change From Baseline Over Time

Abbreviations: CI, confidence interval; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core Questionnaire; VGPR, very good partial response.

CONCLUSIONS

- **Although not statistically significant, zanubrutinib was associated with a higher VGPR response rate compared with ibrutinib in the primary analysis**
  - Additional 5-month follow-up showed a higher VGPR response rate by investigator assessment (intention-to-treat, 30.4% vs 18.2%; *P*=0.0302)
  - No CRs were observed
  - Deeper and sustained IgM reduction over time (descriptive two-sided *P*=0.04)
  - Major response rates were comparable, with directionally favorable PFS, OS, and QoL
- **Zanubrutinib demonstrated clinically meaningful advantages in safety and tolerability**
  - Lower risk of atrial fibrillation/flutter compared with ibrutinib (2.0% vs 15.3%; descriptive two-sided *P*<0.05)
  - Lower rates of major bleeding (5.9% vs 9.2%), diarrhea (20.8% vs 31.6%), and hypertension (10.9% vs 17.3%)
  - There was no difference in the rate of infection despite higher rates of neutropenia with zanubrutinib
  - Fewer AEs leading to death, treatment discontinuation, or interruption were observed with zanubrutinib

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DISCLOSURES

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